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A Journal of Neurology

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PART I., VOL. 35.

Original Articles and Clinical Cases.

THE CYTO-ARCHITECTURE OF THE CEREBRAL CORTEX OF A HUMAN FŒTUS OF EIGHTEEN WEEKS.

BY JOSEPH SHAW BOLTON, M.D., D.Sc., F.R.C.P.,

AND

JOHN MURRAY MOYES, M.B., Ch.B., D.P.M.

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I.—INTRODUCTION.

Of late years much progress has been made in the study of the cyto-architecture of the cortex cerebri and of cerebral function. In 1905 and 1907, Campbell [6] and Brodmann [4] respectively published complete maps of the various areas into which the human adult cerebral cortex may be divided, and further details together with similar maps dealing with the cortex of certain orders of the mammalia have been published both by them and by other workers, notably by Mott [9], Mott and Kelley [10], Mott and Schuster [11 and 12], Watson [14].

As far as we are aware, however, no systematic study of the early evolution of the cyto-architecture of the human cortex cerebri has hitherto been attempted.

On different occasions during the past twelve years, reference has been made by one of us (J. S. B.) to the characteristic features of the cortex of fœtuses and infants, and to the manner in which this structure becomes laminated and develops. In 1900 [1] a description was given of the cortex of the visual area (both visuo-sensory and visuo-psychic) of a child of 3 months, and of a case of anophthalmos of the age of 1 month. In both these cases the visuo-sensory area was mapped out. It was shown that in the case of the former the visuo-sensory area was relatively large in extent, though normal in distribution, whilst in the latter this area was deficient both in extent and in distribution, and its cortex exhibited a similar thinning of the outer layer of granules (Layer IIIa), and of the line of Gennari (Layer IIIb), to that which occurs in cases of long-standing blindness. It was further shown that an almost exact correspondence obtains between the thickness of the conjoined first and second layers of the cortex and the existing degree of amentia or dementia.

In 1903 [2] a description was given of the mode of development of the cortex of the prefrontal area, based on observations made on fœtuses of different ages, stillborn children and infants. It was shown that definite lamination appears in the prefrontal region at about the sixth month of fœtal life, by separation off of the innermost neuroblasts from the remainder. In other words the cortex develops from within outwards. When lamination is completed the cortex consists of the following five primary laminæ, of which two are mainly fibre-laminæ, and three mainly cell-laminæ: (1) *Outer fibre-lamina* or superficial layer; (2) *outer cell-lamina* or pyramidal layer of nerve-cells; (3) *middle cell-lamina* or layer of granule-cells; (4) *inner fibre-lamina* or inner line of Baillarger, and (5) *inner cell-lamina* or layer of polymorphic cells. These observations were confirmed by Watson in 1907 [14], and Brodmann's monograph which was published in the year 1909 [5] contains certain illustrations of fœtal cortex which agree in every histological respect with the features above referred to.

In 1910 [3] this description was amplified and elaborated, and it was pointed out that, whilst the cortex generally evolves from within outwards, that of the visuo-sensory area (sensory projection cortex) develops before that of the visuo-psychic zone (cortex of lower association), and the latter evolves before the cortex of the prefrontal region (cortex of higher association).

Whilst it is not necessary for our present purpose to give further details with regard to these investigations, it may be remarked that in spite of their incompleteness they have served as a key for the elucidation of the structure of the cortex cerebri in the various types of mental disease, from the idiot on the one side of the scale to the dement on the other, and to enable a general pathology of mental disease to be indicated as a broad generalization of amentia and dementia on a basis of cortical sub-evolution and dissolution.

Though not germane to the subject, reference must not be omitted to the classical work of Flechsig [8] on cortical localization, since this has so largely served as the basis of the more modern researches in this subject. Whilst these myelinogenetic observations of Flechsig, and the more recent researches of the Vogts, have furnished valuable information for correlation with the results of the study of the cyto-architecture of the adult cortex, they are without bearing on the early evolution of the cerebral cortex, as lamination and histological differentiation occur at a much earlier date than does myelinization.

The observations on the mode of evolution of the cortex of the fœtus to which reference has just been made have enabled certain general laws of development to be stated. They are, however, not sufficiently complete to enable detailed statements to be made with regard to the early evolution of the cortex and to the histologically differentiable areas which first make their appearance.

II.—Material and Methods.

We have endeavoured in the present research to fill this gap from the aspects both of cyto-architecture and of cortical localization. The facts which determined our choice of a brain for these purposes are as follows: In a fœtus of six months Betz-cells are present, and the prefrontal region, which is of very late development, has begun to laminate. In a fœtus of a little more than four months slight indications of differentiation of neuroblasts exist in the prefrontal region, but no definite evolution of lamination has occurred here.

For the study of the early evolution of the cyto-architecture of the human cerebrum, a brain, therefore, from a fœtus of about eighteen weeks—i.e., a trifle older than the last just referred to—seemed most likely to be productive of useful results.

The evidence on which is based the age of the fœtus we have employed is as follows:—

The fœtus when extended measured 25 cm. in length. When flexed as *in utero* the length from the vertex to the tip of the sacrum was 14·25 cm. The fingers were distinct and separate, and the nails had appeared. The scalp was covered with downy hair, but no hair whatever was apparent on the body. The mouth was open. The membrana pupillaris was present. Ossification had not begun in the os calcis or in the pubic bone. Small centres of ossification were found in the upper two sacral segments. The gall-bladder was formed. It was relatively thick, and the cavity was small, but apparent. A slight fold was noticeable at the ileocæcal junction, but the valve was not present. The kidneys were of about the size of a small hazel-nut, and measured 23 mm. in length by 8 mm. in width. The sex was definitely determinable, the fœtus being a female.

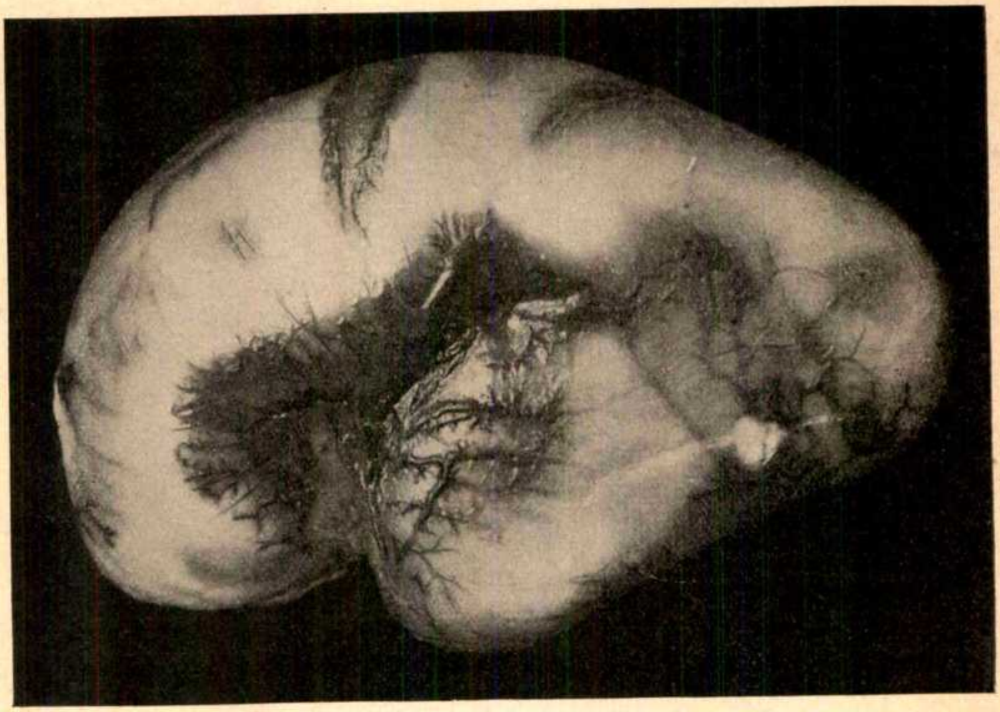

FIG. 1.—Two diameters. Unstripped left hemisphere of human fœtus of the age of eighteen weeks.

As at this age the brain, even when hardened, is of the consistence of soft jelly or blancmange, considerable difficulties were met with which, without proving unsurmountable, nevertheless rendered the study of the hemispheres less complete than was at first hoped. Unfortunately it is impossible in a research of this particular kind to fill in the gaps by employing another exactly similar brain. This is the case on the one hand because it would, to say the least, be very difficult to duplicate a brain of a particular age; and on the other because, as one of us has experienced, great differences exist in the degree of development of two brains which are apparently of exactly the same age. These are in fact so marked as to render futile any attempt to fix in an exact manner the various stages of early cortical development.

The brain was hardened in formalin *in situ*, the skull bones of the vertex being first removed. After a preliminary hardening the brain was carefully floated into a separate dish of formalin. The examination was conducted by the only really satisfactory method in our experience, that of piecemeal blocking—the pia-arachnoid being retained as long as possible in order to keep the fragile hemispheres from breaking up, and the blocks being cut under fluid. The latter were embedded and cut in paraffin, and the sections were selected by counting and stained by the polychrome and iron-alum-hæmatoxylin methods. The former method was found to demonstrate the Betz-cells in a beautiful manner, whereas the latter was of value owing to the permanent nature of the results obtained by means of it, since it is quite easy with experience to interpret such sections in terms of the more elegant but less permanent polychrome specimens.

III.—Anatomical Description of the Cerebrum.

The fissuration of the hemispheres under description agrees with the fœtal measurements already given in indicating an age of about eighteen weeks.

Externally the insula is very large, the fronto-parietal (superior frontal and parietal) operculum is nearly horizontal, and the (inferior) frontal operculum makes almost a right angle with the former anteriorly, and the temporal operculum one of full 60° with it posteriorly. The orbital surface of the frontal lobe, therefore, points almost directly forwards.

Above the posterior third of the fronto-parietal operculum and occupying the middle trisection of the external surface is a short *furrow of Rolando*, which is a distinct fissure in its upper part and a superficial groove in its lower. It is of interest that the Rolandic angle is almost a right angle.

The outer surface of the hemisphere is therefore much less developed than is that of Symington's [13] fifth-month fœtus, which shows a smaller insula, a longer and more oblique furrow of Rolando, and also pits representing the superior and inferior precentral sulci and (?) the parallel.

On the internal aspect, part of the *sulcus cinguli* is present as a shallow ∧-shaped furrow. Posteriorly, the *stem* of the *calcarine fissure* is very evident in both hemispheres as a deep and distinct fissure. In the right hemisphere a (temporary) parieto-occipital fissure is well marked, and in the left a mere trace of the latter is present. The left hemisphere is thus (as is usual) slightly ahead of the right in its degree of evolution.

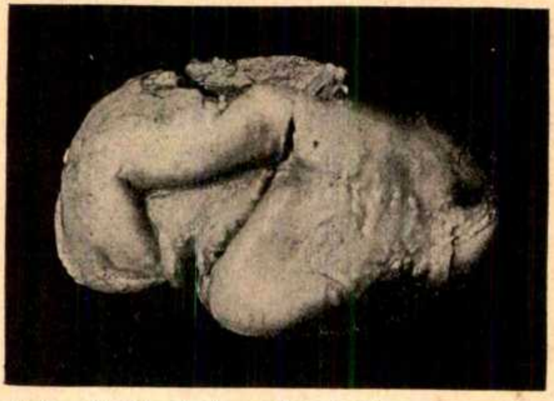

FIG. 2.—Natural size. Left hemisphere stripped. The cracks, and particularly the site near the upper edge from which blocks have been removed, indicate the fragile condition of the tissue.

Owing to the numerous descriptions of the calcarine fissure which are given by different anatomists, it is desirable to state that we here follow that given by one of us (J. S. B.) [1], under which it is described as consisting of three subdivisions—a *stem*, a *body* which consists of the two cuneo-lingual annectants and the part between them, and a *posterior extremity*. This subdivision of the fissure is justified for the purposes of description by the usual large size of the posterior cuneo-lingual annectant, and the frequency with which this is superficial, thus separating off the posterior extremity of the calcarine sulcus from the remainder. The primary division into a *stem* and a *posterior* portion is, however, the correct one, as it is founded on an earlier embryological basis.

In the brain under description, the *stem* is the portion of the fissure which is present.

The following brief account of the development of the calcarine fissure is derived from the classical description of Cunningham [7]. Towards the end of the second or the beginning of the third month of intra-uterine life the precursors of the parieto-occipital and calcarine fissures appear synchronously, and include the primitive cuneus. These primary parieto-occipital and calcarine fissures shortly afterwards disappear, leaving, however, intact the portion which later on becomes the stem of the calcarine sulcus, and which is thus one of the primary fissures of the cerebrum. "This portion alone assumes the responsibility of maintaining the intra-ventricular elevation which results in the calcar avis. Between the fifth and seventh months of intra-uterine life a secondary sulcus appears, as 'two' punctate depressions, one on the occipital pole and the other midway between this and the hinder part of the anterior calcarine fissure or stem. These deepen and then show a tendency to run towards each other in a horizontal direction." The anterior of these depressions soon becomes the deeper, and later on joins the stem, the point of junction being visible in adult life as the anterior cuneo-lingual annectant. The junction between the posterior depression and the rest of the fissure occurs much later, and in many adult brains, and commonly in the negro, the underdeveloped brains of certain of the insane, and the fœtus, it never takes place at all, the posterior extremity remaining usually as a short vertical fissure in the region of the pole of the hemisphere. When, as is usually the case, the junction takes place, the site of this is indicated in the adult brain by the posterior cuneo-lingual annectant gyrus.

The reason for this somewhat detailed description of the structure and mode of development of the calcarine fissure will become clear when the visuo-sensory area is under description, as this presents certain interesting features which can only be explained satisfactorily on developmental grounds.

In the following account of the results of our histological examination, we shall first indicate the limits of such cortical areas as we have been able to define, and shall then give a detailed description of the cyto-architecture of the cortex of these areas and of certain other regions in which it has been possible to recognize a differentiation of structure.

Under these respective headings we purpose to describe:—

(*a*) The limits of the Betz-cell and visuo-sensory areas.

(*b*) The cyto-architecture of

(1) The precentral (Betz-cell) cortex.

(2) The post-central cortex.
(3) The cortex of the visuo-sensory area.
(4) The cortex of (part of) the gyrus cinguli.
(5) The cortex of the anterior frontal region.

IV.—THE LOCALIZATION OF THE BETZ-CELL AREA.

The discovery of Betz-cells in a fœtus of eighteen weeks came as such a surprise that the fact that we were able with relative ease to map out the area containing them seemed commonplace.

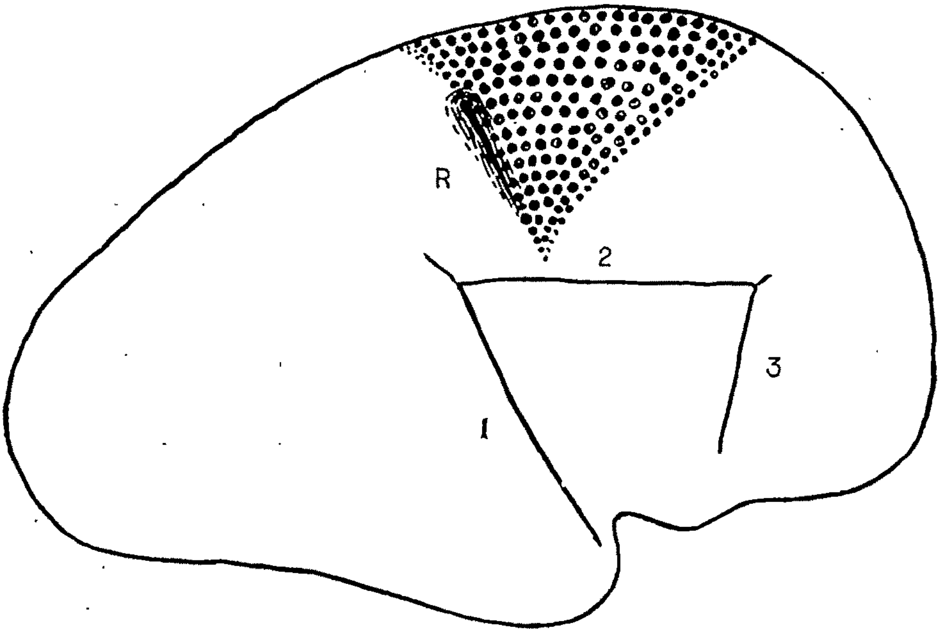

FIG. 3.—Two diameters. Outer surface of right hemisphere. The Betz-cell area is mapped out in dots. The small dots indicate where the area shades into the neighbouring cortex, a sharp line of demarcation existing elsewhere. R, furrow of Rolando: 1, temporal operculum; 2, fronto-parietal (superior frontal and parietal) operculum; 3, (inferior) frontal operculum.

This area is shown in figs. 3 and 4. It is fan-shaped in distribution, the stem of the fan commencing just above the posterior point of trisection of the fronto-parietal operculum, and the upper portion extending considerably over the border of the hemisphere, and in its hinder part involving and passing slightly beyond the sulcus cinguli on to the gyrus of this name.

On the external surface (fig. 3) the posterior edge of the fan in its middle third almost coincides with the bottom of the furrow of Rolando, the Betz-cells extending just posterior to the mid-line of the furrow in many sections.

The area is sharply defined throughout with the exception of three regions. The stem shades downwards to a point concurrently with a decrease in the size and number of the Betz-cells; and anteriorly and posteriorly at the upper angles of the fan, as is shown by the smaller dots on the diagram, the characteristic cortex undergoes some degree of shading into the cortex beyond. This is more evident anteriorly than posteriorly (fig. 4), and it is permissible to assume that this shading indicates that the evolution of the area is not yet complete at the sites where it occurs. The reasons for this interpretation will be given during the description of the visuo-sensory area.

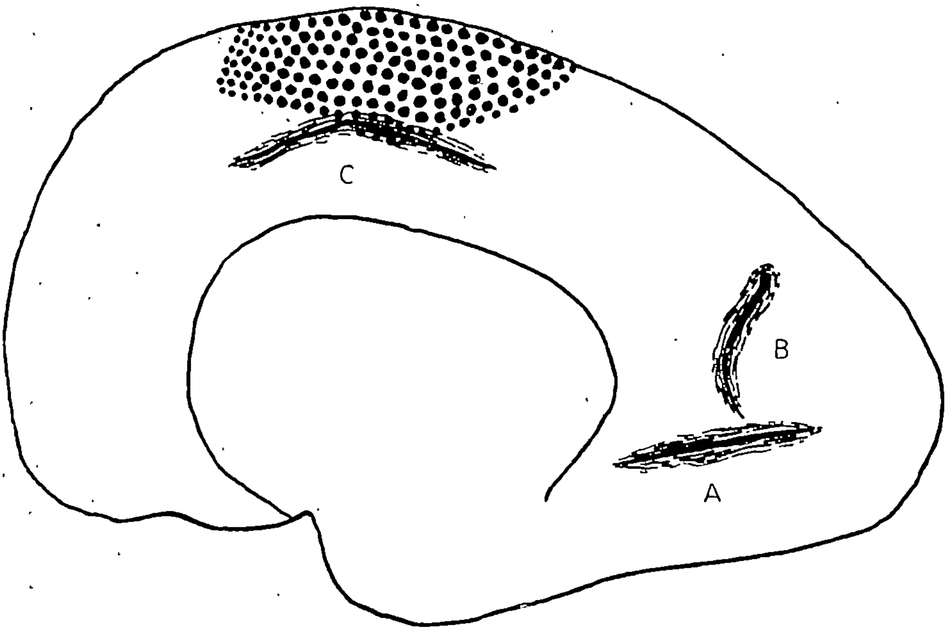

FIG. 4.—Two diameters. Inner surface of right hemisphere. The Betz-cell area is mapped out in dots. The small dots indicate where the area shades into the surrounding cortex, a sharp line of demarcation existing elsewhere. A, (permanent) stem of calcarine fissure; B, parieto-occipital (temporary) fissure; C, fissura cinguli.

Certain features of this somewhat peculiar Betz-cell area are worthy of remark. Its large size in relation to the hemisphere merits comparison with its very early appearance. Its position with regard to the furrow of Rolando is so characteristically human as to afford a useful illustration of the truth that in the complex of phylogenetic and ontogenetic factors which subserve the process of evolution, the latter from a very early period play a predominant part. Lastly, to trench for a moment on more purely histological details, the high evolution of this region as a well-defined cortical area, at a time when such adult guiding lines as the furrow of Rolando and the sulcus cinguli are merely indicated, is surely proof positive, even to a prejudiced observer, that, as one of us long ago suggested, lamination and histological differentiation precede fissuration. The latter must therefore be regarded as a probable—in many instances, perhaps, a merely possible—consequent on the former.

V.—THE LOCALIZATION OF THE VISUO-SENSORY AREA.

The limits of the left visuo-sensory area are indicated on fig. 5.

As has already been remarked, the stem of the calcarine fissure (A), which remains a permanent feature of the fissural system, is present, whereas the temporary parieto-occipital fissure (B) has almost disappeared. No indications are yet present of the pits which later form the body and the posterior extremity of the calcarine fissure.

The visuo-sensory area is pear-shaped, in many respects resembling the appearance of this area in the adult. At its anterior extremity, it commences on the lower lip of the stem of the calcarine fissure, and as it extends backwards it spreads so as to involve also the upper lip. Almost from its commencement it extends downwards well beyond the inferior lip of the stem of the calcarine fissure. Not, however, until just before it passes beyond the stem of the calcarine fissure into the unfissured cortex behind this, does it extend upwards beyond the line of the upper lip of the calcarine fissure. This area in many respects resembles in distribution the visuo-sensory area of a case of anophthalmos of the age of one month, which was published by one of us (J. S. B.) many years ago [1]. It thus produces belated evidence that the latter is not a freak of development, but actually represents the distribution and extent of the visuo-sensory area at some period of evolution which is slightly ahead of eighteen weeks of intra-uterine development, and which is probably the period at which in this particular case of anophthalmos evolution ceased.

The visuo-sensory area under description presents the following special features.

It is in a much earlier stage of development than is the Betz-cell area already described. Its existence as a cortical area is, in fact, determined, not by any special features of cyto-architecture beyond the preliminary cleavage of neuroblasts, but by its characteristic situation, extent and distribution.

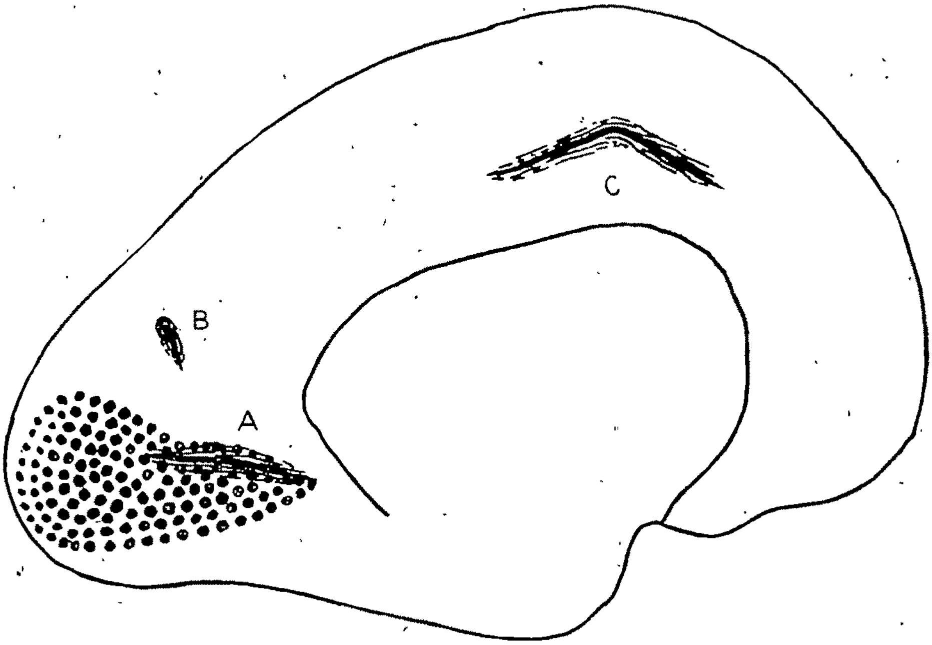

FIG. 5.—Two diameters. Inner surface of left hemisphere. The visuo-sensory area is mapped out in dots. Posteriorly, as is indicated by the smaller dots, it shades into the surrounding cortex. A, (permanent) stem of calcarine fissure; B, parieto-occipital (temporary) fissure; C, fissura cinguli.

In degree of development, and in actual depth of cortex, the part in relation to and below the stem of the calcarine fissure is by far the best part of the area. Posteriorly to the fissure, the cortex is much thinner, and towards the hinder limits of the area some degree of shading into the surrounding undifferentiated cortex occurs. It is, therefore, quite evident that development is proceeding from before backwards, as three grades of this exist, namely, the anterior good part in relation with the stem of the calcarine fissure, the middle thin part behind the fissure, and the posterior part which shades backwards. The fact that development has not yet occurred far, either histologically or from the point of view of distribution, may probably be correlated with the fact that the visuo-sensory area, in relation to the hemisphere as a whole, is proportionally smaller than is the Betz-cell area.

As with the Betz-cell area, so in the case of the visuo-sensory area, it is clear that lamination and histological differentiation of the area precede fissuration, for in this case the area is determinable, although the body and posterior extremity of the calcarine fissure are not due to develop for a considerable time.

VI.—THE CYTO-ARCHITECTURE OF THE CORTEX.

A description will now be attempted of the various types of lamination which we have been able to define in the cortex of the brain under investigation. The more definite of these will be illustrated by microphotographs. With regard to the latter it is desirable to point out that, owing to the thinness of the cortex, and to the crowding of this with small cells, it has been necessary to enlarge the specimens to the unusual degree of 133 diameters. This has been done by means of a long extension apparatus, since the lenses at our disposal did not permit of any other method of displaying the whole of the cortex in each specimen. The results, though good for the method, are hence not as satisfactory us we could wish; and the subdivision of the microphotographs into laminæ is much less definite in the illustrations than is the lamination in the actual specimens.

(1) *The precentral* (*Betz-cell*) *cortex.*—The cortex of the Betz-cell area is composed of neuroblasts which as yet, apart from the Betz-cells, are embryonic and indifferent as regards structure.

Beneath the outer fibre-lamina (L.I), which approximately occupies one-seventh of the total depth, is the outer cell-lamina (L.II), arranged as irregularly-columnar rows of cells placed vertical to the external surface. No middle cell-lamina (L.III) is apparent, as is to be expected in an agranular region. The outer cell-lamina (L.II), also in depth occupying about one-seventh of the cortex, is separated from the inner cell-lamina (L.V) by the broad inner fibre-lamina (L.IV), which in its lower part contains the Betz-cells. The chief feature which distinguishes the inner fibre-lamina from the superjacent and subjacent cell-laminæ is the sparseness of the scattered and irregularly placed cells which it contains. This lamina is somewhat deeper than is the subjacent inner cell-lamina, occupying about three-sevenths of the total depth, whereas the latter occupies little more than two-sevenths of this. The Betz-cells thus lie less than two-thirds of the depth of the cortex from the surface, whereas in the adult they lie at a depth of about three-quarters. In other words, in this fœtus these cells lie in a position which is intermediate between their respective positions in the cortices of the dog and the rhesus.

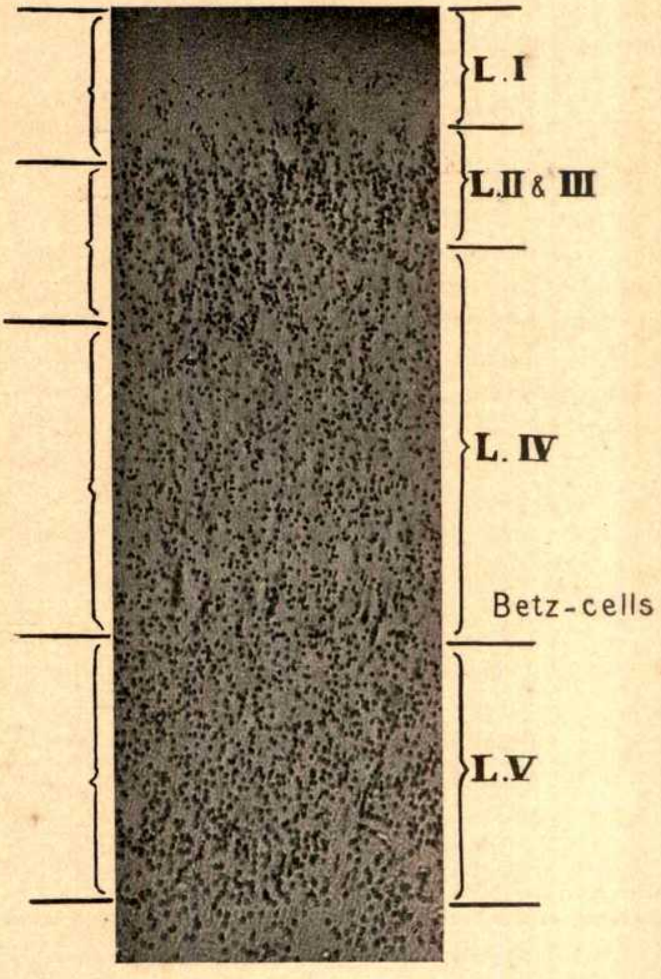

FIG. 6.—One hundred and thirty-three diameters. The precentral cortex. L.I, the outer fibre-lamina; L.II and L.III, the outer cell- or pyramidal-lamina, and the middle cell- or granule-lamina; L.IV, the inner fibre-lamina, which contains a layer of Betz-cells in its lower part; L.V, the inner cell- or polymorphic lamina.

As is illustrated in fig. 6, the Betz-cells lie in groups in every way similar to those seen in the adult cortex. They however differ somewhat in shape and size from adult cells. In sections stained by the same method, an ordinary large adult Betz-cell measures on the average 30 μ by 50 μ. The Betz-cells under description vary in length from 29 μ to 36 μ, and are about 7 μ in width at the base. The nucleus, which is very constant in size, measures about 5·5 μ in diameter. Compared with adult cells, these cells are therefore relatively narrow and pyramid-shaped. As is well shown in the illustration (fig. 7), they are large and conspicuous objects, and are as readily visible in a well-stained section as are normal Betz-cells. Their topographical distribution is similar to that in the adult, the largest cells lying in the neighbourhood of the upper border of the hemisphere.

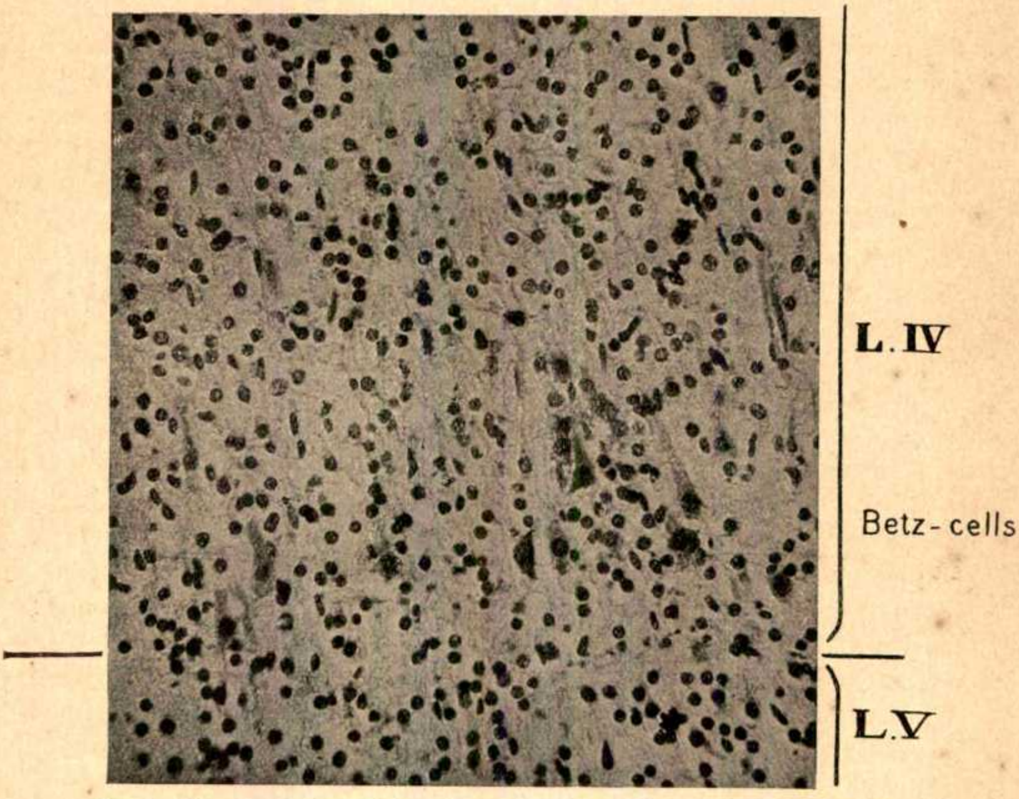

FIG. 7.—Three hundred and eighty diameters. The precentral cortex. L.IV, the lower part of the inner fibre-lamina, containing Betz-cells near its bottom; L.V, the upper part of the inner cell- or polymorphic lamina.

As has already been remarked, the Betz-cells extend backwards over the anterior lip and wall of the furrow of Rolando to the bottom of the fissure, and in several sections they may be seen extending backwards to just beyond this point. We have ourselves seen single Betz-cells extending to just beyond the bottom of the furrow of Rolando in more than one adult brain, and therefore regard the above relationship of the Betz-cells to the furrow of Rolando as within the normal limits. It is, however, only right to state that Campbell, in his monograph, remarks, "It is important to note that the cortex under consideration does not extend quite to the floor of the fissure" (of Rolando) "in any part." During the descent of the mammalian scale it is well known that the Betz-cell area reaches backwards to a decreasing extent. Whether our own or Campbell's views are correct with regard to the adult relationship of the area to the furrow of Rolando, it is nevertheless certain that the distribution in the fœtus under investigation is in this respect human rather than subhuman, which is the point we wish to emphasize.

(2) *The post-central cortex.*—In the immediate neighbourhood of the furrow of Rolando (posterior wall and posterior lip of the fissure), the whole depth of the cortex is thickly strewn with cells, so thickly in fact that the lamination is obscured. There is, however, a vertical columnar arrangement of the cells to be seen in the upper sixth or so of the total cell-depth, and the lower quarter or so of the total depth of cells tends to be separated from the rest as the inner cell-lamina. This region is extremely difficult to subdivide into laminæ, but we have satisfied ourselves that the lamination marked out in the illustration (fig. 8) is correct. According to this the outer fibre-lamina (L.I) occupies about one-sixth of the total depth, the outer cell-lamina (L.II) occupies a similar depth, the middle cell-lamina (L.III) occupies about one-third of the total depth, the inner-fibre-lamina (L.IV) occupies a a twelfth or less, and the inner cell-lamina (L.V) completes the cortex. Whether this interpretation of the lamination is correct or not, the marked preponderance of cells, compared with their relative sparsity in the pre-Rolandic cortex, is strongly suggestive of the probability that this cortex is concerned with the performance of sensory-projection functions. As the latter is *known* to be the case, it is likely that our interpretation of the lamination is correct, although in this particular case such interpretation must be regarded as an opinion rather than a certain observation.

More posteriorly the type of lamination alters and becomes more definite. Here the outer fibre-lamina (L.I) is of course evident. Below this the upper half of the remainder is occupied by the outer and middle cell-laminæ (L.II and L.III). The greater and more superficial part (L.II) tends to be columnar, and the lesser and deeper part tends to be diffuse (L.III). The deeper part of the cortex is readily separated into the inner fibre-lamina (L. IV) with very few cells, and the deeper inner cell-lamina (L.V) with numerous cells.

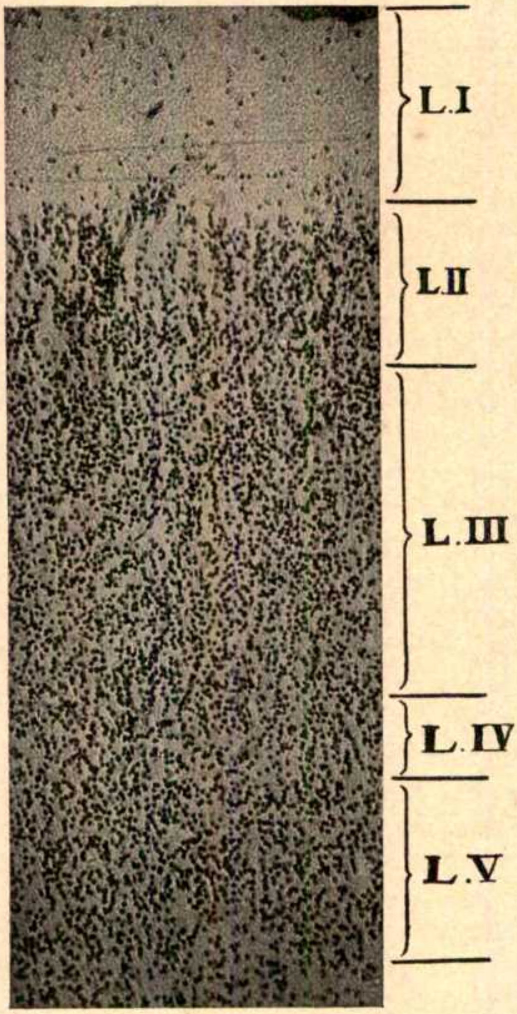

FIG. 8.—One hundred and thirty-three diameters. The post-central cortex. L.I, the outer fibre-lamina; L.II, the outer cell- or pyramidal lamina; L.III, the middle-cell, or granule-lamina; L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

It is hardly necessary to point out to a reader familiar with the diagrams of Campbell and of Brodmann, especially the latter, that the pre- and post-central cortices of this fœtus of eighteen weeks present appearances which, immaturity being allowed for, are identical with those of the normal adult. The precentral Betz-cell area is efferent, psychomotor or cerebral-associative-motor, and corresponds with "4," if not also "6," of Brodmann, and with the "precentral," if not also the "intermediate pre-central" of Campbell. The post-central cortex on the other hand corresponds with "3," "1" and "2" of Brodmann and shades backwards into "5," "7" and "40," and, in the case of the diagram of Campbell, with the "post-central" and "intermediate post-central," shading backwards into the "parietal" of this observer. The attempted compromise made by one of us [3] between the views of Brodmann and Campbell on the one hand and the "bodily sensibility projection area" of Flechsig on the other thus fails when the necessary information is available. It was regarded as possible that during early fœtal development the general sensory projection area might not occupy the identical site in which it lies in the adult, in which case Flechsig's inclusion of the precentral gyrus, &c., in this area might be true, since his researches were conducted by the method of myelogenesis. In view, however, of the evidence which we have adduced with regard to the cyto-architecture of the precentral and post-central cortex in a fœtus of eighteen weeks, it is certain that even at this early period of development the normal adult structure is already laid down. It is necessary therefore to conclude that Flechsig's areas "1," "1a," "1b," and "6" do not correctly represent the "bodily sensibility projection area" in the fœtus. Area "1" and the posterior part of area "1b" together must be regarded functionally as earlier and later afferent-projection regions, and area "1a," and the anterior part of area "1b," together with area "6," must similarly be regarded functionally as earlier and later efferent-projection regions. This *must* be the case, since the afferent and efferent cortical regions are well differentiated with regard to their future functions at a period long prior to that at which myelogenesis commences. We do not, however, wish to impugn the correctness of the observations of such a master in research as Flechsig, and therefore suggest a further and more probable explanation of his results.

In the brain under description, the pre- and post-central regions are far and away the best developed parts of the cortex. It seems reasonable to us to assume that this remarkable development of the cortical part of the great sensori-motor machine at such an early period of evolution bears a definite relationship, from the aspect of ontogenesis, to the already stable condition of the lower reflex mechanisms. The latter truth is of course evidenced by the reflex movements of the fœtus *in utero*, which about this period of development not only are active, but also are readily felt by the mother. Since the sensory or afferent fibres to the cortex in all probability develop before the motor or efferent fibres from the cortex, it is certainly *possible* that the former may be distinguishable from the latter by the study of their myelogenesis, but it is extremely improbable. In fact, since the efferent cortical fibres originate from the Betz-cells, and have a considerable

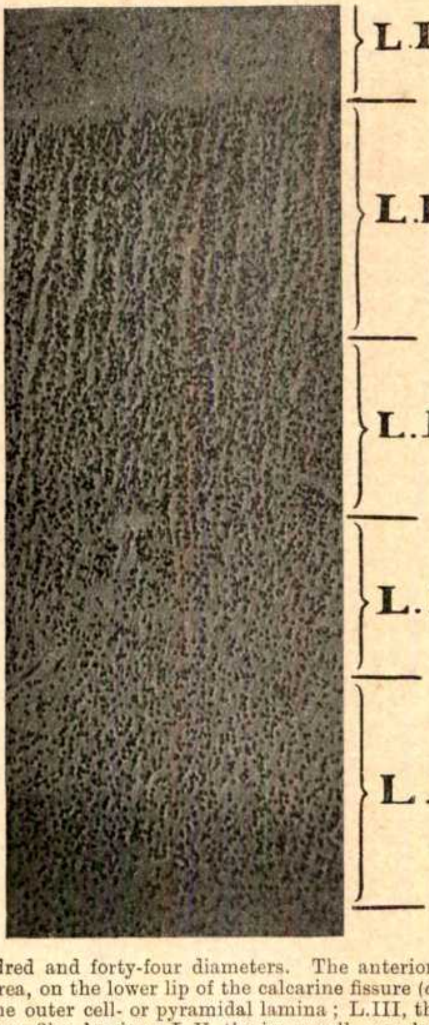

FIG. 9.—One hundred and forty-four diameters. The anterior, and best developed, part of the visuo-sensory area, on the lower lip of the calcarine fissure (*cf.* fig. 10). L.I, the outer fibre-lamina; L.II, the outer cell- or pyramidal lamina; L.III, the middle cell- or granule-lamina; L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

distance to travel, whereas the afferent cortical fibres do not travel uninterruptedly, it is extremely unlikely that at any period of fœtal development it is possible to make an absolute distinction between such afferent and efferent fibres. It is thus possible to accept the results of Flechsig as correct, without at the same time accepting the conclusions which he draws from them, and especially is this the case since the cortex, from the neuronic aspect, is so well developed at a period long prior to the commencement of myelogenesis. We would remark, in order to escape the criticism that the above observations are purely theoretical, that they are inserted with the sole object of defending a renowned investigator, whose researches have served as the origin, if not as the basis, of the fruitful work of the past twenty years.

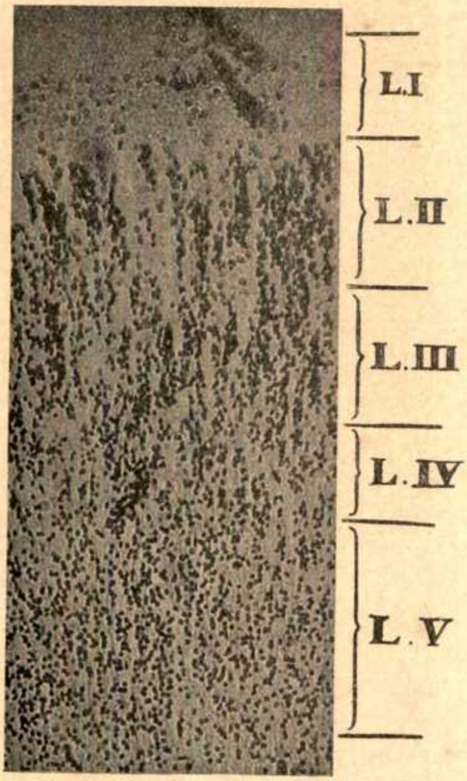

FIG. 10.—One hundred and thirty-three diameters. The posterior, and less well-developed part of the visuo-sensory area (*cf.* fig. 9). L.I, the outer fibre-lamina; L.II, the outer cell- or pyramidal lamina; L.III, the middle cell- or granule-lamina; L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

(3) *The cortex of the visuo-sensory area.*—Throughout this area, which is in a very early stage of development, the distinguishing feature is a cleavage of the neuroblasts owing to the development of the inner fibre-lamina, which cleavage allows of the mapping out of an area possessing, as has already been indicated, all the characteristic features of extent and distribution of the adult visuo-sensory area. As has been stated, the anterior part of the area, namely, that related to the existing stem of the calcarine fissure, is the best developed, the posterior portion being, however, exactly similar in type, though thinner and in an earlier stage of evolution. The anterior and posterior portions are respectively illustrated in figs. 9 and 10. The outer fibre-lamina (L.I) is obvious, and the inner fibre-lamina (L.IV) is in the anterior part (fig. 9) equally definite, though not quite so obvious in the posterior portion of the area (fig. 10).

Between these laminæ is a mass of neurones, which together represent the outer and middle cell-laminæ (L.II and L.III). The former part consists of cells which are arranged in vertical columnar bundles, which shade downwards into the diffusely arranged cells of the middle cell-lamina (L.III). Below the inner fibre-lamina (L.IV) is the inner cell-lamina (L.V), which is composed of an aggregation of smaller cells lying closely packed. The cells of this lamina are smaller and less embryonic in structure than are the rest of the cells of this part of the cortex, in accordance with the general law under which the cortex laminates and develops from within outwards.

The lamination of the posterior part of the visuo-sensory area is identical, with the exception of the fact that the cortex is thinner and the separation into laminæ is not quite so obvious.

Surrounding the visuo-sensory area is a type of cortex which we take to represent the visuo-psychic, since the features presented by it allow of this deduction.

Its lamination is as follows: The outer fibre-lamina (L.I) is as usual. The outer cell-lamina (L.II) is deeper than the corresponding lamina of the visuo-sensory area, but is similarly composed of cells lying in vertical columnar bundles. The middle cell-lamina (L.III) is much narrower than the corresponding lamina in the visuo-sensory area and is difficult to define, as it practically constitutes the lowermost part of the lamina above it in this region. The inner fibre-lamina (L.IV) is shallower and much less evident than the corresponding lamina of the visuo-sensory area, but is quite visible. It contains many fewer cells than the latter. Finally, the inner cell-lamina (L.V) is much shallower than the corresponding lamina of the visuo-sensory area and its constituent cells are on the whole slightly larger and more embryonic.

(4) *The cortex of the gyrus cinguli.*—The portion of the cortex of this gyrus, which is illustrated in fig. 11, is that below the anterior extremity of the Betz-cell area. In the brain under description this region is at the anterior part of the gyrus cinguli, and in an adult brain the homologous region would probably be about the middle of the gyrus.

Between the Betz-cell area and the cortex of the cingulate gyrus lies an intermediate type of cortex which will first be described. The outer fibre-lamina (L.I) shows nothing unusual. Below this, for about one-third of the rest of the depth of the cortex, and representing the outer and middle cell-laminæ (L.II and L.III), lie vertical columns of embryonic cells. The inner fibre-lamina (L.IV), with relatively very few contained cells, lies below this mass of cells, and below it again is the inner cell-lamina (L.V), which is fairly broad and very definite, and consists of a mass of well-developed cells. This type of cortex extends from the Betz-cell area down over the upper lip of the cingulate fissure, across the bottom of this, and up the lower lip. It is here replaced by the cortex of the cingulate gyrus, which contains fewer elements and is of very different structure, and obviously older, as is shown by the more developed and less embryonic appearance of its constituent cells.

The structure of this cortex (fig. 11) is as follows: The outer fibre-lamina (L.I) is of the usual appearance and occupies about one-eighth of the depth of the cortex. Below this lies the conjoined and inseparable outer and middle cell-laminæ (L.II and L.III). This conjoined lamina is very narrow, occupying but one-eighth of the depth of the cortex. The cells are arranged in vertical columns, and are very embryonic in appearance and possess large nuclei. Below this comes the broad inner fibre-lamina (L.IV), which occupies no less than three-eighths of the depth of the cortex. It contains scattered cells of pyramidal type which are better developed than those above them and possess rather smaller nuclei. The remaining three-eighths of the cortex consist of the inner cell-lamina (L.V). This lamina is very well developed and contains numerous cells which are smaller and older than those above them and possess much smaller nuclei. In brief, the characteristic features of this type of cortex are the very high evolution of the inner cell-lamina (L.V), the good development of the

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inner fibre-lamina (L.IV), and the very poor evolution of the middle and outer cell-laminæ (L.II and L.III).

(5) *The cortex of the anterior frontal region.*—The chief feature of the anterior frontal cortex is its extreme thinness. At the same time, however, there are definite indications of a cleavage of the neuroblasts slightly below their middle (fig. 12).

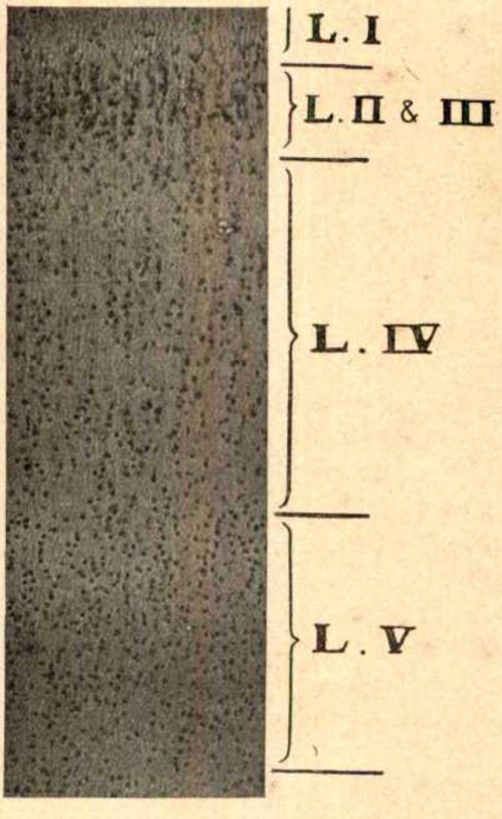

FIG. 11.—One hundred and thirty-three diameters. The cortex of the gyrus cinguli below the anterior part of the Betz cell area. L.I, the outer fibre-lamina: L.II, the outer cell- or pyramidal lamina; L.III, the middle cell- or granule-lamina: L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

The arrangement of the neuroblasts is irregularly mixed rather than vertically columnar, in the upper part, and the very common pairing or quadrupling of the neuroblasts, &c., indicates proliferation of probably all the elements, whether capillaries, neuroglia or neuroblasts. In some cases rows of as many as six elements suggest the columnar arrangement of cortex of later development. This appearance, though by no means entirely peculiar to the anterior frontal region of this case, is much more marked and definite here than elsewhere. The cortex thus consists roughly of four portions, of which the first and third are rather less deep than the second and fourth. The first is the outer fibre-lamina (L.I). The second is the precursor of the outer and middle cell-laminæ (L.II and L.III). The third represents the inner fibre-lamina (L.IV), and the fourth is the inner cell-lamina (L.V).

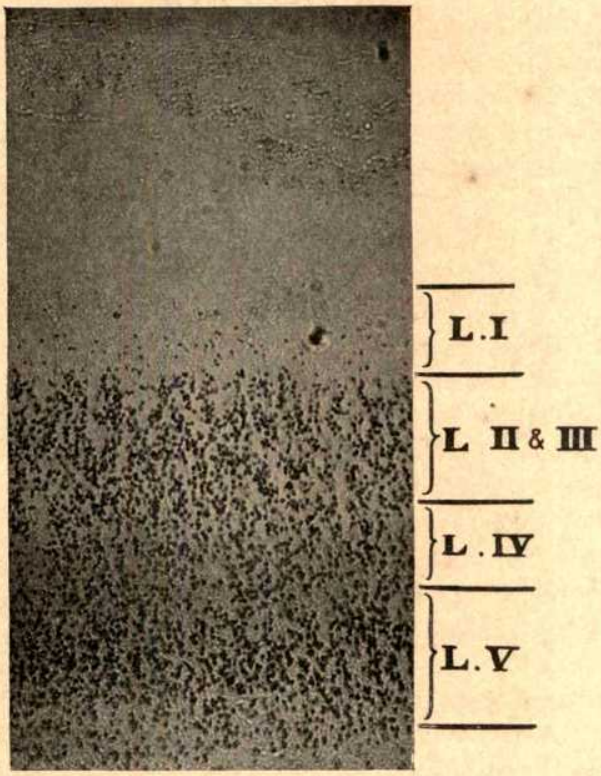

FIG. 12.—One hundred and thirty-three diameters. The very embryonic anterior frontal cortex. L.I, the outer fibre-lamina; L.II, the outer cell- or pyramidal lamina: L.III, the middle cell- or granule-lamina; L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

The characteristic feature of this type of cortex is the fact that all the neuroblasts are equally embryonic, the inner cell-lamina (L.V) being as under-developed as the middle and outer cell-laminæ (L.III and L.II). The anterior frontal cortex thus markedly contrasts with the cortex of the cingulate gyrus, an obviously, and well-known, earlier type, in which L.V is very well developed, L.IV is well developed and L.III and L.II are very poorly evolved.

VII.—SUMMARY.

By the histological examination of the cerebrum of a fœtus of eighteen weeks we have arrived at the following results (amongst others) :—

(1) Considerable progress has already occurred with regard to the specialization of cortical areas and the differentiation of neuroblasts.

(2) The Betz-cells are well developed, and the relatively very large Betz-cell area can be accurately mapped out.

(3) The visuo-sensory area can be defined with accuracy. In the case of this area, however, specialization of the cortex and differentiation of the neuroblasts are both less advanced.

(4) The pre- and post-central cortices and the visuo-sensory area already possess the adult relationships to the Rolandic and calcarine fissures respectively.

(5) The pre- and post-central cortices are remarkably well evolved in comparison with the rest of the cortex.

(6) The cingulate cortex is of poor quality but is relatively well advanced in development.

(7) The anterior frontal cortex, on the other hand, is throughout its depth extremely embryonic in structure.

(8) There is very definite evidence that, in the complex of phylogenetic and ontogenetic factors which subserve the process of evolution, the latter from a very early period play a predominant part.

(9) The cleavage of the developing neuroblasts of the cortex into upper and lower portions, which enclose between them the precursor of the inner line of Baillarger, takes place at a much earlier period than we have hitherto supposed. This is clear, since this line (L.IV) is indicated in the rudimentary anterior frontal cortex, and since the Betz-cells which are contained in it in the pre-central region are so well developed.

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A CASE OF GENERALIZED STREPTOTRICHOSIS WITH EXTENSIVE LESIONS IN THE CENTRAL NERVOUS SYSTEM.

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THE case recorded here derives its interest mainly from the lesions found in the brain and meninges, streptotrichial infection in this region being an occurrence of some rarity. Howard [11], writing in 1903, finds only eighteen cases in the literature. A case reported by Delépine [7] in 1889 is not included in Howard's list, which gives details of all the eighteen cases, and from which many of the following particulars have been obtained, and since 1903 two further cases have been described, one by McDonald [13] in 1904, and one by Beevor and Buzzard [4] in 1903.

If we include the case under consideration the total number of recorded cases is twenty-two.

Considering these in a little more detail we find that in five cases the lesions in the central nervous system were described as primary, that is, no further lesions of a streptotrichial nature were discovered, while in the remaining seventeen cases lesions of a similar nature were found elsewhere in the body.

The lesions found in the central nervous system consisted of cerebral abscesses, almost always multiple, and meningitis.

In thirteen cases cerebral abscesses were present without meningitis.

In three cases the meninges were affected without abscess formation.

In six cases both abscesses and meningitis were present.

The abscess formation observed in these cases shows considerable similarity of character, and need not be further noticed here. With regard to those cases in which the meninges were affected, however, the lesions seem to have differed considerably.

Thus in a case recorded by Almquist [2], on the true nature of which Howard throws considerable doubt, the lesion found was a cerebrospinal meningitis.

Dolore [8] records a case in which a cerebrospinal pachymeningitis of streptotrichial origin was the only lesion present.

In Beevor and Buzzard's [4] case a basal leptomeningitis was present, and this was the type of meningeal lesion found in the present case, and in the remaining cases described, excluding a case described by Ponfick [14] in which the lesion commenced extracranially and perforated the skull, producing a localized meningitis and abscess formation.

Batten [3], writing on meningitis, says: "Streptothrix infection of the meninges is a rare condition. It is most commonly found as an extension from a focus in the skull or soft parts of the face and throat, but some cases of primary infection have been recorded. Sometimes true metastatic foci have been found in the meninges secondary to infection in other parts of the body."

On examining the nine cases mentioned above, however, we find that in two cases only has infection of the cranial bones been noted, namely, one case reported by Ponfick [14] and alluded to above, and the case described by Beevor and Buzzard [4] in which caries of the sphenoid was found.

In Almquist's [2] doubtful case the meningeal lesion was considered as primary, while in the remaining six cases the meningitis was part of a more general infection.

Thus in Dolore's [8] case the original lesion was one affecting the neck and face.

In Chiari's [6] two cases the brain lesions were secondary to a streptotrichial bronchiectasis. In Eppinger's [9] case the bronchial and supraclavicular glands were primarily affected. In the case described by Keller [12] an abscess in the thoracic wall was the only other lesion present, while in the case under consideration the liver and lungs were the seat of streptotrichosis.

Indeed, if we extend the list to include the remaining thirteen cases, in which the meninges were unaffected, we find no further mention of disease of the cranial bones, so that metastatic infection would seem to be the rule in these cases.

In this connexion certain facts observed in the above cases are of some interest. Thus, dealing with the microscopical features of the organisms present in the twenty-two cases, in seven cases clubs and rosettes are mentioned as being absent or very rare. In only one case, that described by Bollinger [5], were typical colonies with club formation definitely stated to be present, while in the case under consideration very definite club formation was present in the colonies in the central nervous system.

Delépine [7], in describing the lesions present in the case recorded by him says: "In a few vessels bacilli were also found, but it was not possible to determine whether they were adventitious products or not. They looked, however, not unlike segments of the more typical filaments found in the abscesses, and were probably early forms of the organism." No such appearances could be observed in the present case.

In the majority of cases in which an accurate description of the organism is given it is described as consisting of a few branching thread forms, sometimes in twisted masses, usually showing little beading and with a marked absence of club formation.

Dealing briefly with the relative frequency of streptotrichosis of the central nervous system as compared with a similar condition in other parts of the body the following figures taken from an article by Acland [1] may be given. Duvan, writing in 1902, and quoted by Acland, gives the following details of 257 cases:—

Face and neck	70	Central nervous system	19
Thorax	65	Generative organs	19
Liver	40	Œsophagus	7

In the same article Acland gives the following table showing the situations of the lesions in 109 cases of streptotrichosis occurring in the United Kingdom between the years 1884 and 1906:—

Abdomen (including liver)	68	Brain and spinal cord	5
Face, neck, tongue, &c.	50	Acute general	9
Chest	29		

The case under immediate consideration will now be described, and finally a few special points in connection with it considered.

While in the hospital the patient was under the care of Dr. Hawkins, and later of Mr. Makins, and it is through their kindness that I am enabled to record it here.

The patient, a man, aged 45, by trade a horsekeeper, was admitted to St. Thomas's Hospital on January 31, 1911, with a large tender swelling in the lower part of the abdomen, and gave the following history.

On January 7 he first noticed a feeling of tenderness over the lower part of the abdomen. No swelling was then present. A few days afterwards a small hard swelling appeared, which gradually increased in size. The tenderness and pain continued, and were increased after a heavy meal or on coughing.

The patient stated that he had never vomited, but that he had always suffered from a slight tendency to constipation.

Inquiries as to his family history yielded no information of importance. The only facts of interest in his past history were as follows:

He contracted syphilis at sixteen years of age. The chancre was followed by a rash, but no further lesions developed.

From 1886 to 1903 patient served in the Army, and from 1886 to 1889 was stationed in India, where he had repeated malarial attacks.

He had lost "about a stone" in weight during the six months preceding admission.

The following was the state on admission:

The heart, lungs, and nervous system were all found to be normal. The urine showed nothing abnormal.

A tumour could be seen and felt, occupying the hypogastric region, and extending slightly into the umbilical and left iliac regions.

The percussion note over the tumour was impaired; the tumour possessed well-defined edges; it did not pulsate; no fluctuation could be made out, and the skin was nowhere adherent over it. The swelling increased in size, and a week after admission the skin over its most prominent part became adherent, and fluctuation was felt.

On the eighth day the patient, who had been running an irregular temperature, varying between normal and 102° F., had a rigor, and the temperature rose to 103·5° F.

The following day an incision was made into the swelling, and about half a pint of foul-smelling pus of a yellow colour was removed, and the cavity drained.

The pus was examined in the Clinical Laboratory, and returned as sterile.

About the same time the patient's serum was tested for the Wassermann reaction with a positive result.

The wound continued to discharge for seven weeks, during which time the patient's condition showed little change, and then, on April 1, he had another rigor, the temperature then returning to the slightly irregular course, varying between 97·5° F. and 100° F., which it had followed since the first operation.

The blood was examined for malarial parasites without result. A count of the white-cells revealed a leucocytosis of 16,600 per c.mm.

On April 24 an exploratory laparotomy was performed. The appendix was found behind the cæcum. It was about 5 in. long, and showed signs of old disease, but there was no obvious connexion between it and the abscess in the anterior abdominal wall. It was removed.

This operation was followed by a temporary improvement in the condition of the patient, but on April 12 he had another rigor, and the temperature continued of a pyæmic type until June 6, accompanied by frequent rigors.

On May 15 the percussion note over the base of the left lung was noted as impaired, and a few crepitations were audible in this region. These signs gradually extended, and eventually involved the greater part of both lungs.

A frequent cough developed with expectoration, and an examination of the sputum revealed the presence of elastic fibres.

A blood culture taken about the same time was found to be sterile.

From June 6 to June 23 the temperature remained at a lower level, never rising above 101° F.; but on June 17 patient had a series of fits beginning in each case with clonic movements of the left arm and leg, which then became generalized, and were succeeded by a period of rigidity. The patient became noticeably cyanosed during these attacks, and on several occasions bit his tongue. Unconsciousness usually lasted for ten to fifteen minutes, and after regaining consciousness the patient usually slept for several hours.

These attacks were repeated on June 18 and 19.

On July 3 paralysis was first noticed affecting the left arm and leg, and more marked in the former.

Both knee-jerks were slightly exaggerated.

The right planter reflex was extensor, the left indefinite. On the same date the patient was noted to be suffering from a left hæmianopia.

Two days later incontinence of urine and fæces developed, the paresis became more profound, and the patient died on July 8. Frequent rigors occurred from June 23 to the time of death.

Post-mortem Examination.

The *post-mortem* examination revealed the following conditions. Scars indicating the incision into the abscess and the laparotomy were present. The lower end of the former scar still showed a red granulomatous area.

On opening the abdominal cavity the intestines immediately adjacent to the laparotomy scar were found to be adherent to the abdominal wall, but the peritoneal cavity appeared otherwise healthy.

The liver.—Throughout the upper part of the right lobe were scattered 12 to 20 small white nodules varying in size from about ½ in. in diameter down to the size of small shot. The smaller of these were of comparatively firm consistence, but the larger were breaking down in the centre, and on pressure yellowish pus exuded. No granules were present.

The lungs were riddled throughout with small shotty nodules having about the same range of size as those seen in the liver, but the smaller considerably predominating. All the larger and most of the smaller nodules yielded on pressure pus of the same type as that found in the liver, and here again no granules could be seen.

The brain.—The base was covered with thick yellowish pus over an area extending from the under surface of the cerebellum posteriorly to the optic chiasma anteriorly. The pus did not reach to the lower

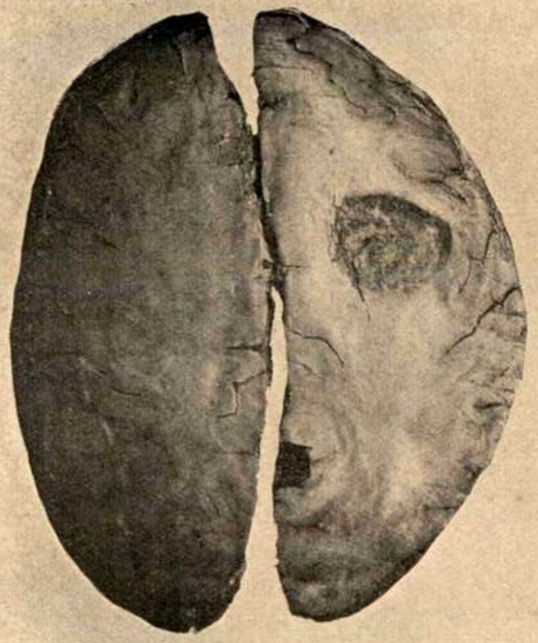


FIG. 1.—Showing a large single abscess lying beneath the right ascending frontal convolution. A small portion of brain-tissue has been removed from the right occipital lobe for microscopical examination.

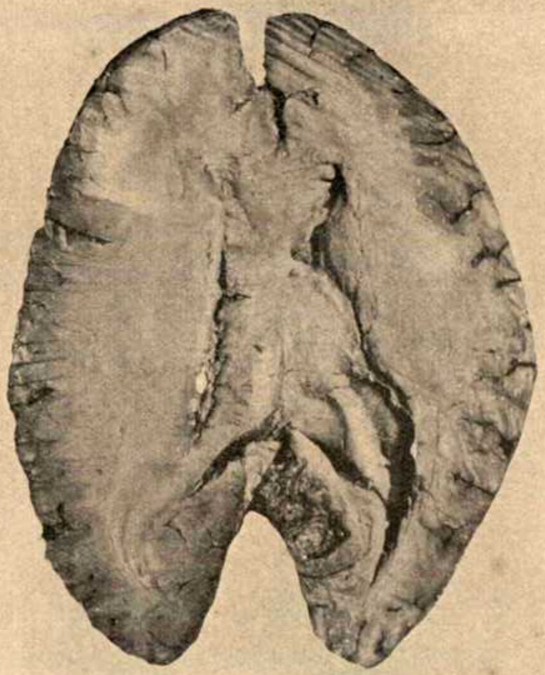


FIG. 2.—Showing a smaller more irregular abscess situated in the right occipital lobe just anterior to the calcarine fissure.

part of the medulla, or upper part of the cervical cord; the remainder of the cord was not removed.

The obvious deformity of the brain revealed the presence of extensive suppuration within its substance; one large abscess indeed burst during examination, but only a minute quantity of pus escaped.

The brain was then hardened for twenty-one days.

The spleen was large, dark red in colour, and of soft consistence.

The appendix had been amputated.

The kidneys, heart, intestines, and remaining organs showed no naked-eye changes.

After hardening, the brain was further examined, with the result that the following areas of suppuration were discovered (figs. 1 and 2).

(1) A large, single, irregular abscess-cavity lying deep to the upper half of the right ascending frontal convolution, right Rolandic fissure and right ascending parietal convolution and extending forwards beneath the hinder part of the superior and middle frontal convolutions.

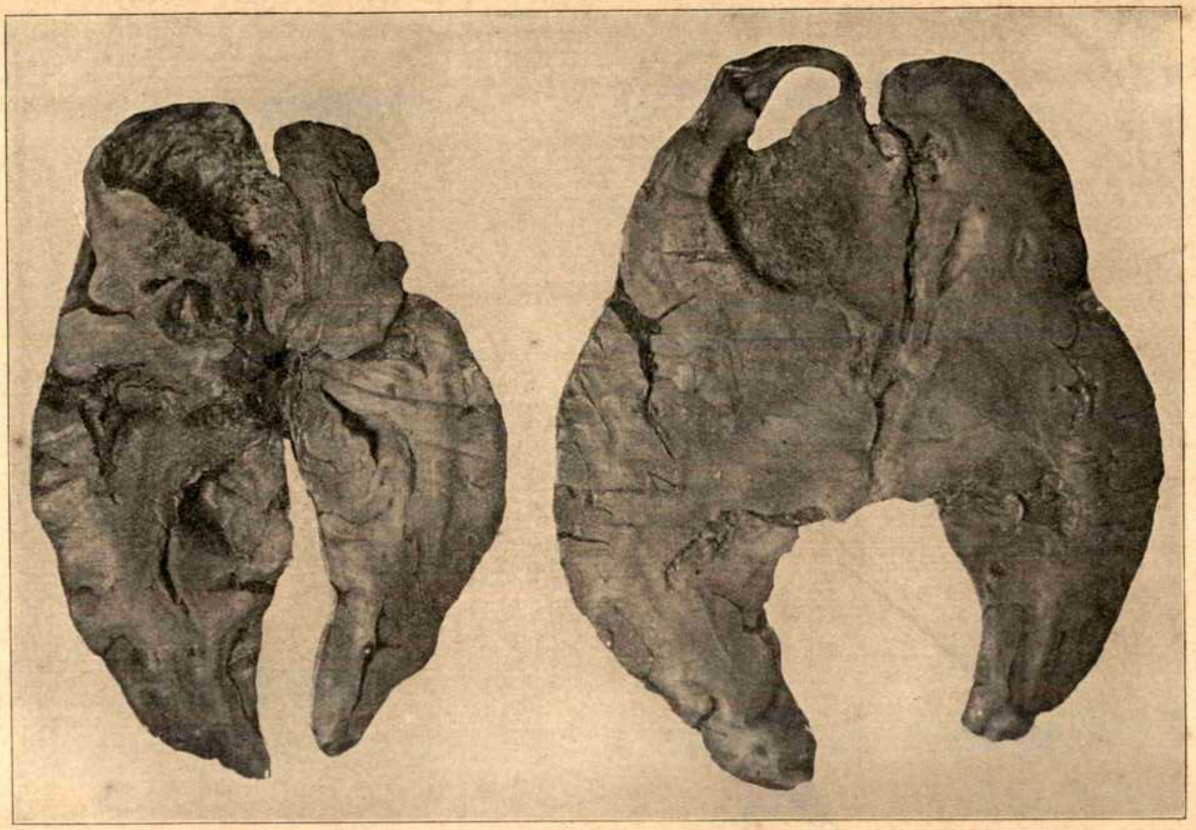
In its lower part it lay altogether in the white matter, in its upper part the cortex itself was excavated, and in one place, in the upper half of the right ascending frontal convolution, only a very thin shell of cortex covered the cavity (figs. 3 and 4).

(2) A smaller, more irregular and somewhat loculated abscess situated in the right occipital lobe just anterior to the calcarine fissure, the cortex in the neighbourhood of which was extensively invaded.

(3) A very large, multilocular abscess, consisting of two large pockets and many smaller ones affecting the left frontal lobe, which was very largely destroyed. This cavity was much distended with pus, and the right frontal lobe was markedly displaced and compressed as a result of the enlargement of the opposite lobe. Scattered around this large abscess cavity were many small foci of suppuration, not directly connected with the main cavity.

The pus in all these abscesses was of the same type as that observed in the liver and lungs, and though granular débris was present no bodies of the "mustard seed" type could be observed. The walls of the cavities were ragged and showed no attempt at encapsulation. On opening the ventricles they were found full of a slightly turbid fluid, but sections taken from the various parts of their walls showed no evidence of extension of the disease in this direction.

Microscopical sections were prepared from the liver, lungs, cerebral tissue and meninges; tissue being chosen in each case, which, to the naked eye, appeared to be in the earlier stages of the disease—i.e., the



FIGS. 3 and 4.—Showing a large multilocular abscess situated in the left frontal lobe. The two main cavities communicated through the aperture seen in the right-hand figure. Note the extreme deformity of the whole right hemisphere, especially the frontal lobe.

sections passed through the smaller foci where breaking down of tissue and pus-formation was least advanced. The sections were stained by Gram's method in each case.

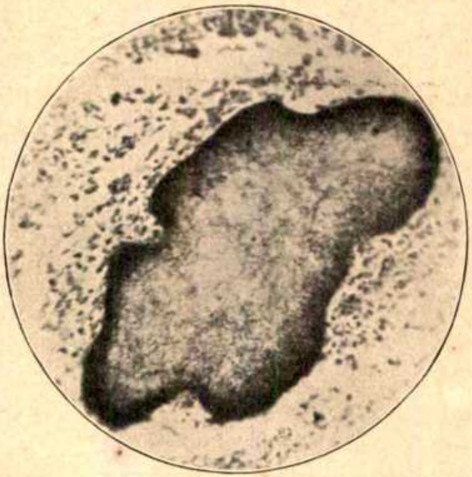


FIG. 5.—A streptothrix colony from a section obtained from the liver. Note the complete absence of radial clubs.

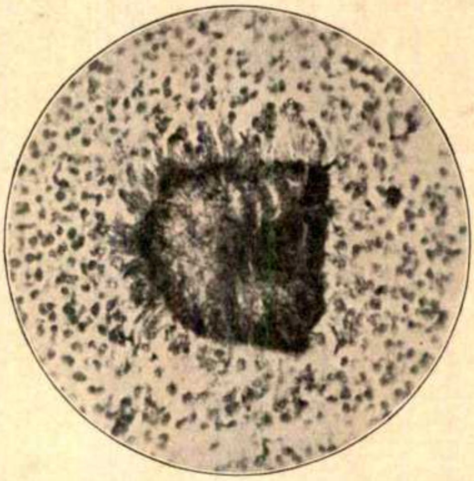


FIG. 6.—A streptothrix colony from a section obtained from the wall of a cerebral abscess. Note the well-marked radial clubs.

Typical colonies of a streptothrix were obtained in a certain number of sections from all the lesions.

A remarkable difference, well shown in the accompanying microphotographs, was observed between the colonies in the brain and those elsewhere. (Figs. 5 and 6.)

Whereas the colonies in the liver, for instance, showed the appearances usually found in human streptotrichosis, with little or no attempt at radial club formation, the colonies in the cerebral lesions showed the most marked radial club-formation, resembling that seen in the bovine disease, save that in no case did these clubs retain the stain by Gram's method.

The threads themselves showed marked beading in almost every case, and many coccus-like bodies were present in the majority of colonies.

The cellular reaction was largely of the mononuclear type, with a considerable admixture of polymorphonuclear cells in most cases.

An attempt was made to cultivate the organism from the pus from the liver abscess, but only a mixed staphylococcic growth resulted. The cultural characteristics could not, therefore, be made out, and it is impossible to relegate the organism to any special class.

One of the main points of interest in this case is, perhaps, the question of the original site of infection.

The appendix was found at the operation placed retro-cæcally, and was slightly thickened and fibrosed. The thickening was slight only, and there was no sign of any caseative or suppurative process, that is, the organ showed none of the lesions which are usually associated with streptothrix infection in this region. But Foulerton [10] says, "The tendency to natural cure must also be remembered as a possible explanation of cases in which streptotrichial lesions occur only in parts which would seem not liable to become the seat of a primary infection from without; thus in a single focus of infection in the liver it is always possible that there may have been a primary infection of some part of the intestinal canal, the initial lesion having meanwhile become healed."

It is thus possible that the condition of the appendix represented an old, healed streptotrichial lesion.

The next question is whether the abdominal abscess was of the same nature.

There are two facts which point in the opposite direction: (1) In the course of the examination of the pus from this abscess which was sterile on culture, the possibility of actinomycosis was thought of, and the organism searched for with negative results; (2) although streptotrichial lesions may heal under certain conditions, this is true, in most cases, only of slight lesions; and it is certainly exceptional for a streptotrichial lesion of the extent of the abscess noted to heal as completely as was the case in this patient.

The obvious alternative is that the abscess was in reality a breaking-down gumma, and additional weight is given to this view by the history of syphilitic infection and the presence of a positive Wassermann reaction.

Whatever the seat of the primary infection, there seems no doubt in this case that the final distribution occurred viâ the blood-stream, and was of the nature of a true pyæmia.

The reason of the marked radial club-formation is by no means obvious.

The cerebral lesions were certainly terminal in character, and it is improbable that they were of long standing. A clue is perhaps afforded by some further remarks of Foulerton's [10]; after pointing out that infection seems usually to be spread in the body by short rod segments which then branch and not by the spore forms, where further development would occur in the typical radial manner, he says, "In some circumstances, as when a suppurating cavity in the lung is in communication with the air, spore forms may be present in abundance, and being conveyed elsewhere may doubtless originate fresh foci of infection."

In this case the clinical findings make it almost certain that the pulmonary lesions preceded the cerebral.

CONCLUSIONS.

The case here recorded presented extensive lesions in the central nervous system, consisting of a basal lepto-meningitis, and multiple cerebral abscesses.

These lesions were proved to be streptotrichial in nature by the demonstration of colonies of the organism in microscopical sections.

There was no disease of the cranial bones or of the soft tissues of the head or neck, but extensive streptotrichial lesions were found elsewhere in the body. It is therefore clear that the cerebral lesions resulted in this case from an infection of a pyæmic type, and not as the result of extension from neighbouring parts, and a study of the literature would suggest that infection by the blood-stream is the rule in cases of streptotrichosis in this situation.

The colonies of the streptothrix found in the cerebral lesions showed certain marked differences from those found in the liver and lungs, and these differences may, perhaps, be accounted for by the different forms in which the infection may have been carried, in the one case as true spore-forms from the pre-existing pulmonary lesions, in the other as short filaments, which would appear to be the more common method.

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PROGRESSIVE SPINAL MUSCULAR ATROPHY OF INFANTS (WERDNIG-HOFFMANN TYPE).

BY F. E. BATTEN, M.D.
AND
GORDON HOLMES, M.D.

THE following case was under our care in the Out-patient and the In-patient Departments of the National Hospital, and was exhibited at the Clinical Section of the Royal Society of Medicine on February 10, 1911, as a case of the Werdnig-Hoffmann type of the progressive spinal muscular atrophy of infants.

Some differences of opinion existed at first as to the diagnosis of the case, and it was originally suggested that the condition resembled that described by Oppenheim under the name "myatonia congenita." But though there was considerable loss of tone in the muscles, the marked paresis of the proximal muscles as compared with the distal, and the paralysis of the intercostal muscles pointed to a myelopathic rather than a myopathic disease.

CLINICAL HISTORY.

The patient was the second of two children. The elder, a boy, died at the age of eight months of broncho-pneumonia; the parents described him as loose in his limbs and more or less similarly affected. No other instance of nervous disease was known in the family.

The patient was first seen in the Out-patient Department of the National Hospital in June, 1910, when she was 1 year 2 months old. She was born at the seventh month and had been delicate during the first four months of life, but she moved and kicked about as other children till she was about 6 months old. Then she seemed fat and healthy and was able to sit up, but was not encouraged to do so. At this age she was vaccinated and she cut her first tooth, but from this time onwards her parents noticed her becoming weaker and more helpless. At seven months she was able to say a few words. Between nine and twelve months she lost almost all power in her limbs and became unable to sit up, or to hold her head erect when it was unsupported.

When she was first seen she was a well nourished and fairly developed child; all her limbs were weak, especially at their proximal joints, and if she were placed in a sitting posture her back bent under her weight and her head hung backwards or to either side as drawn by gravity. Her limbs were flabby and toneless, but the atrophy of the muscles was obscured by a thick covering of subcutaneous fat. All the deep reflexes were absent. The movements of the eyes, face and tongue seemed unaffected, and the child was bright and intelligent. During the first few months that she was under observation she appeared to her mother to become a little stronger, but in October, 1910, at the age of eighteen months she was reported to be weaker, and then slight muscular contractures in the legs were noticed for the first time.

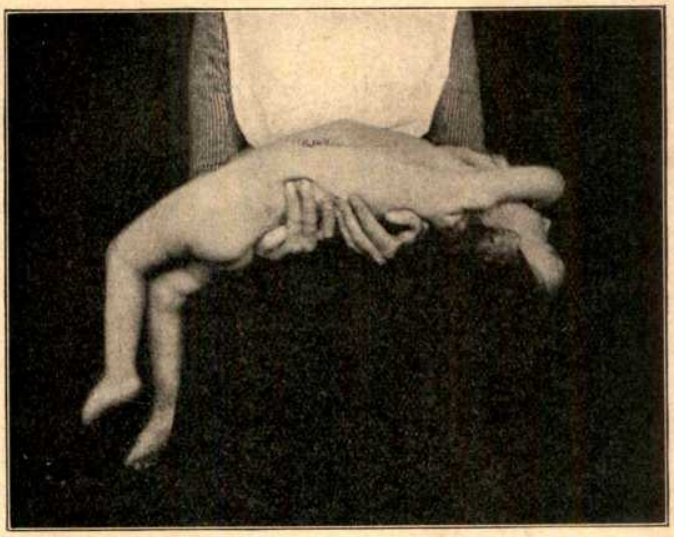

FIG. 1.—Photograph of child lying in nurse's arms showing her "limp" condition and her inability to raise her head or flex her legs.

She was admitted to hospital in January, 1911, at the age of one year and nine months. She was a bright and intelligent child and seemed to take an interest in all around her. She could talk, but it was difficult to understand what she said. She was easily upset and then cried in a normal manner, but evidently with very little breath, each few sobs being followed by an interval in which she made a few deep inspirations with considerable effort. The palpebral fissures were narrow and this gave the child the appearance which had been called "mongoloid," but apart from this there was nothing to suggest that she was a mongoloid idiot. The forehead had a central prominence over the frontal suture, but otherwise the head was normally shaped and measured 19½ inches in circumference. There was no sign of rickets; the incisors, canines and first molar teeth were present.

The movements of the eyes, jaws, tongue and lips were quite normal, and the child swallowed without difficulty. She could also see and hear well, and obeyed commands as far as her muscular power permitted. Her optic discs were normal.

She could not raise her head from the pillow or even turn it from side to side. When placed in the sitting position the head fell backwards, or forwards, or to either side, the neck muscles being almost powerless. Her back also became bent, as there was no power in the trunk muscles either to fix or straighten the spine (figs. 1 and 2). When placed flat in the bed, however, the spine became perfectly straight. The other trunk muscles were equally weak, with the exception of the diaphragm, which contracted vigorously. Her chest was long and narrow, and on each inspiration the intercostal spaces sank in, respiration being almost wholly diaphragmatic. The abdominal muscles though very weak were not completely paralysed.

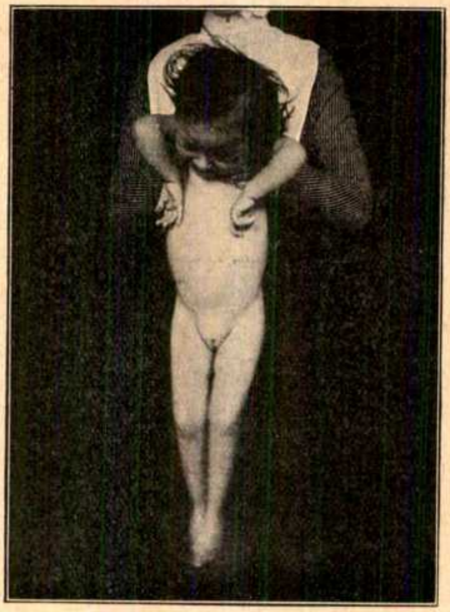

FIG. 2.—Photograph of child held up by a nurse; the head falls forward and the arms tend to "come away" from the trunk.

The arms as a rule lay flexed at the sides of the chest, with the forearms pronated. She could make small movements with the fingers and grasp objects feebly, and could just flex and pronate the elbows, but not supinate the forearms. There was no power of movement however at the shoulder-joints. The lower limbs were almost powerless; practically no movement was possible at the hips or knees, but she had slight power of flexion and extension of the ankles and toes. The hamstrings were slightly contractured, so that the knees could not be fully extended.

The limbs were thin and their muscles much wasted, but this wasting was, to a considerable extent, obscured by subcutaneous fat. The muscles were also toneless, but the feet could not be brought over the shoulders nor the arms crossed behind her back, positions which are possible when there is marked hypotonia in a child.

Electrical examination showed complete loss of response to faradism in all the paralysed muscles, but the muscles of the hands responded fairly well. The child bore strong currents without evincing any signs of pain. In short, the child had an almost complete flaccid paralysis of all the muscles of the neck, trunk and limbs, the muscles of the face, eyes, and the diaphragm alone remaining normal.

Sensation to ordinary stimuli appeared to be unimpaired all over the body. The knee-jerks, ankle-jerks and the other deep reflexes were absent, but the sphincter functions were unaffected.

The child was removed from hospital in April, 1911, and died at home in the following January at the age of 2 years and 9 months.

The *post-mortem examination* was performed in the child's home forty-eight hours after death. There was then no rigor mortis present. The body appeared well nourished and so well covered with fat that the muscular wasting was scarcely apparent. When the skin was incised a thick layer of pale adipose tissue was found, and the muscles of the limbs and of the pelvic- and shoulder-girdles were so small and pale that it was, in certain instances, difficult to recognize them. Further, when they were cut across they were found to be soft and flabby, and the pallor was evidently due to the amount of fat they contained. This flabbiness and pallor of the muscles were more marked in the proximal segments of the limbs than in the distal. The rectus abdominis seemed to be less affected than most of the limb muscles, but the erector spinæ were extremely wasted and pale. The diaphragm was the only muscle which, in naked-eye appearance, approximated to the normal. Portions of a large number of muscles were taken for microscopical examination; they were fixed in Zenker's fluid, and embedded and cut in celloidin.

The larger nerve-trunks appeared unaffected to the naked eye; it could not be said they were smaller than normal. The brain and spinal cord also appeared normal, though the ventral roots of all segments of the cord were remarkably small and slender.

MICROSCOPICAL EXAMINATION.

Nervous system.—The brain, spinal cord and several peripheral nerves were examined by Marchi's and by Weigert-Pal's methods, and in sections stained by hæmatoxylin and van Gieson's picro-fuchsin; several sections of the spinal cord were also stained by Nissl's method.

The Marchi method shows no evidence of either recent or old degeneration in any part of the central or of the peripheral nervous system. The medullated fibres of the medulla oblongata and spinal cord stained well by the Weigert-Pal method, and there is no evidence of degeneration of any of the longer tracts. On the other hand, the staining of the medullated fibres in the grey matter is defective, and the medullated meshwork in the ventral horns is thinner than normal. The ventral roots in both their intra- and extra-medullary courses are small and poorly stained, while the dorsal roots appear normal and stain well. The only definite change that is revealed by this method in the peripheral nerves is an apparent loss of fibres in some of the bundles, while a certain proportion of the fibres that remain are small and poorly stained.

Sections of the spinal cord stained by van Gieson's method show no inflammation or interstitial change, but the most striking feature apparent in sections of all regions is a paucity of cells in the ventral horns, and the small size of those cells which remain. In sections stained by Nissl's method the same remarkable deficiency of ventral horn-cells is even more striking. The small cells show no marked deviation from the normal; they appear like normal cells in miniature. The nuclei and nucleoli are situated centrally, and the chromophilic substance stains well.

All groups of ventral horn-cells are severely affected, but the postero-lateral group in the cervical region is relatively best preserved. This deficiency of cells was confirmed by an enumeration of all those visible in a series of sections 10 μ thick. In fifteen sections from the third lumbar segment, for instance, there was an average of only eight cells in the right ventral horn and 7·7 in the left, while in these fifteen sections only seven large cells were counted, the others being all small. For the same segment of the normal cord, Bruce gives the average number of large cells as forty-seven, and nine small cells per section. Figs. 8, 9, 10 and 11, which are photographs and drawings of sections from the same segments of the cervical regions of the affected and of a normal cord, illustrate very well the deficiency in number and the diminution in size of the ventral horn-cells. The control is taken from the cord of a child, aged 10 months, and therefore considerably younger than the patient. Another normal cord from a child, aged 5, was also compared with that of our patient, and, although there is but little difference in the size and number of cells at these two ages, the comparison with the cord of the younger seems fairer, and this has been consequently reproduced.

The cells of the rest of the grey matter of the spinal cord appear normal in size and number; Clarke's column and the intermedio-lateral cells of the lateral horn seem large and extremely well developed in contrast with the cells of the ventral horns.

Muscles.—The muscles which were removed from the body and have been examined were the trapezius, the pectoralis major, the rectus femoris, the biceps femoris, the rectus abdominis, the erector spinæ, the flexors of the fingers and the diaphragm.

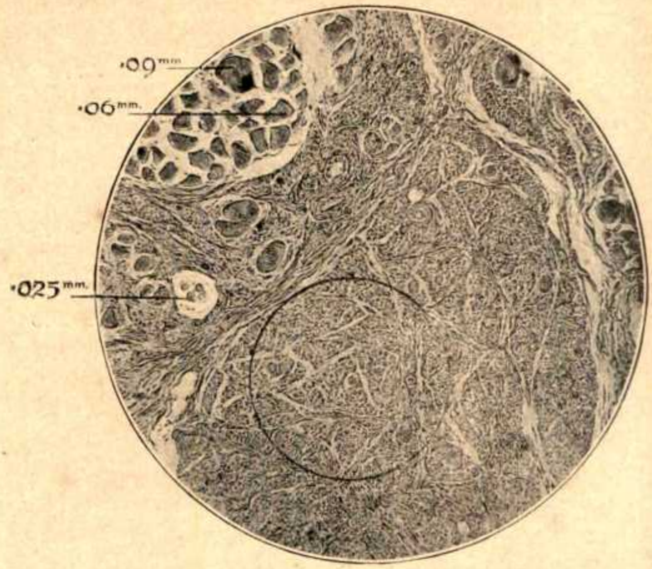

FIG. 3.—Transverse section of pectoralis major muscle, showing general structure of the muscle. A bundle of normal muscle-fibres is seen in the section; these measure from 0·04—0·9 mm. in diameter. Scattered about the section are a few isolated fibres of normal size; but the majority of fibres have undergone extreme atrophy and measure 0·01 mm. and less. A muscle-spindle containing four muscle-fibres is seen, the intra-fusal fibres measure 0·025 mm., which is normal for these fibres. Magnification about 50 diameters.

The small circle indicates the area represented in the more highly magnified fig. 4.

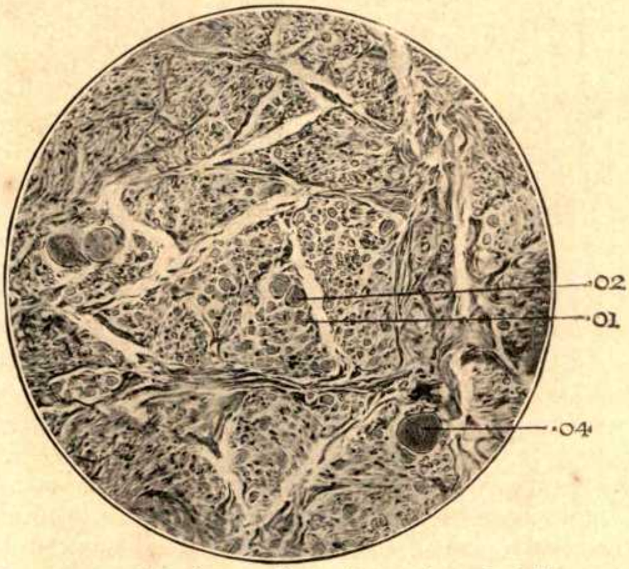

FIG. 4.—Transverse section of pectoralis major muscle under higher magnification. It shows a few comparatively large fibres about 0·04 mm., but most of the fibres measure 0·01 mm., and some as little as 0·003. Magnification about 150 diameters.

There is little or no increase of the connective tissue between the individual fibres.

All these muscles have been cut in transverse and longitudinal sections, and stained by the van Gieson method.

The diaphragm alone of all the muscles examined shows no pathological change.

The changes in the affected muscles are strikingly similar, though they vary somewhat in the degree to which they affect the different muscles. All the muscles show a large number of atrophied or undeveloped muscle-fibres, with a few bundles of well-developed fibres. There is generally an increase in the amount of interstitial fat, and the connective tissue between the bundles is increased, although there is but little or no increase between the individual fibres. The latter feature stands out in rather striking contrast to the condition found in a myopathic muscle.

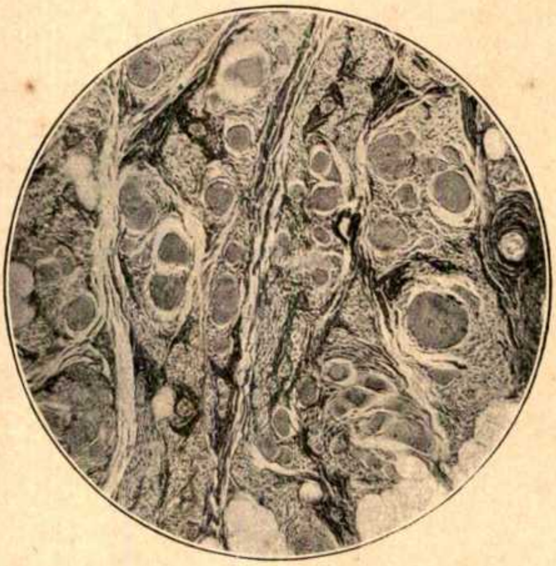

FIG. 5.—Transverse section of biceps femoris showing several large isolated fibres, some of which are surrounded by a number of atrophic fibres. There are numerous bands of connective tissue between the various muscle bundles. Magnification about 150 diameters.

A description of a section of the pectoralis major (fig. 3) will serve as an example of the changes present in all the muscles. In this muscle, bundles of normal muscle-fibres having a polygonal shape can be seen measuring ·06 to ·09 mm. in diameter (fig. 3). In close proximity to such normal bundles are bundles containing fibres of very small size, some measuring as little as ·0025 mm. Between these minute and atrophied fibres and the normal fibres all varieties of sizes are seen. Many of the small fibres are round or oval in outline, and not of the normal polygonal shape in cross-section. In some bundles in which almost all fibres are of small size a few large isolated fibres of a round or oval shape are present measuring ·04 mm. (fig. 4). The nuclei

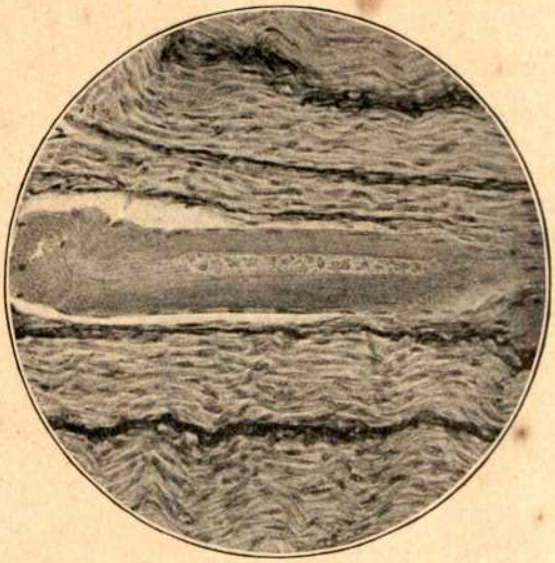

FIG. 6.—Longitudinal section of anterior tibial muscle showing degeneration of the centre of a large muscle-fibre. The neighbouring fibres have undergone extreme atrophy.

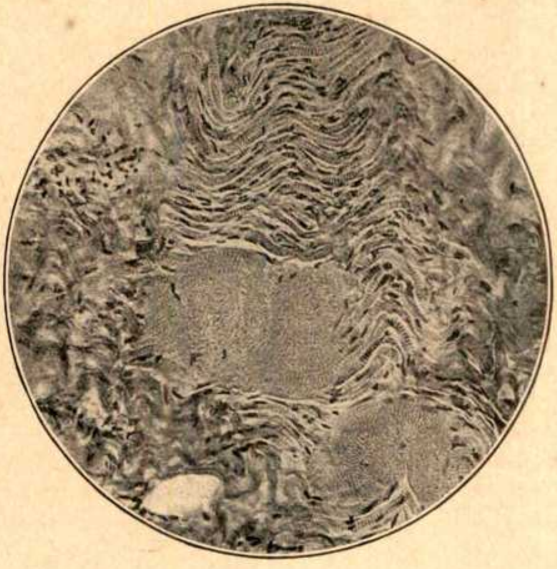

FIG. 7.—Section of rectus femoris muscle showing large fibres splitting into numerous fine fibres. The transverse striation of these small muscle-fibres is well preserved.

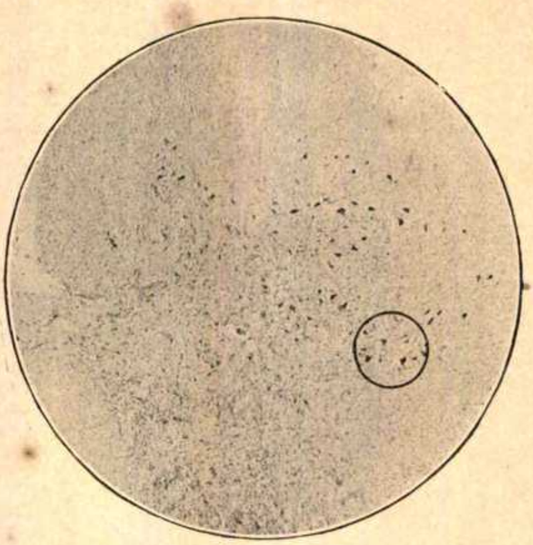

FIG. 8.—Photographs of the anterior horn of the cervical region of the spinal cord of a normal child, aged 10 months, to compare with the fig. 9. The section has been taken from the same segment in the cervical region, and has been similarly stained and photographed under the same magnification. The circle indicates the position of the cells seen under higher magnification in fig. 10.

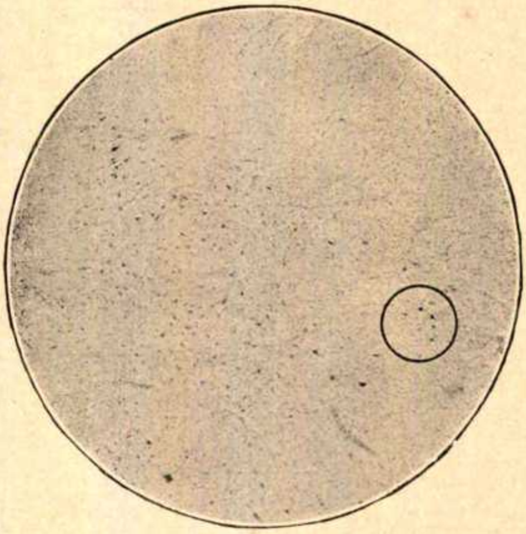

FIG. 9.—Anterior horn of the cervical region of the spinal cord showing the marked diminution in the number of the cells and the small size of those which still remain. The circle indicates the position of the cells seen under higher magnification in fig. 11.

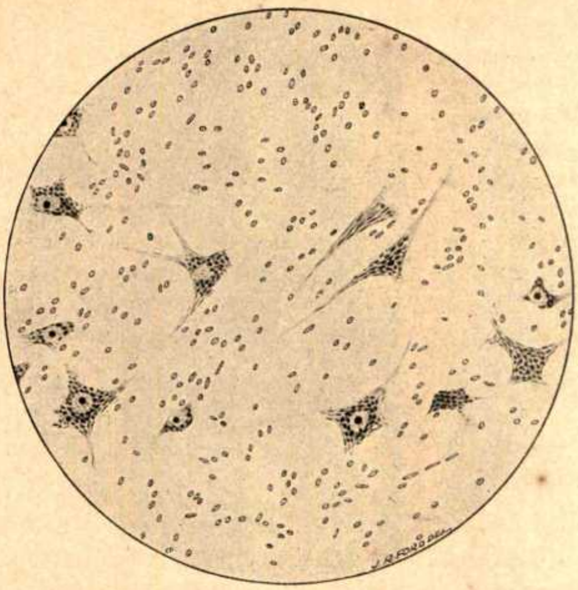

FIG. 10.—Normal cells of the anterior horn under high power (child aged 10 months).

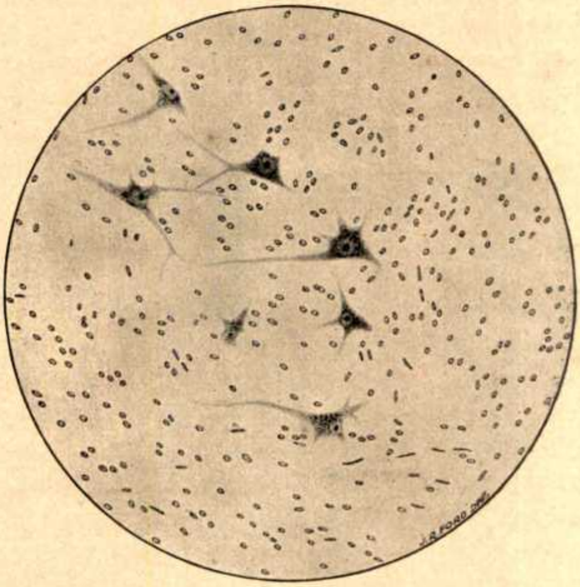

FIG. 11.—Cells of anterior horn under same magnification, showing their relatively small size and comparatively normal appearance.

Figs. 10 and 11 have been reproduced from drawings made from photographs taken under the same magnification.

(Drawings have been used in the place of photographs because of the impossibility of obtaining clear photographs of all the cells in the field.)

of the muscle-sheaths are in most places normal; but in others are grouped together, and form a dark band surrounding certain muscle-fibres.

The connective tissues between the bundles is relatively increased owing to the smallness of the muscle-fibres (fig. 5).

Most of the fibres, even those which are extremely small, show normal transverse striation (fig. 7).

Some few fibres show central degeneration (fig. 6), and some sections show a splitting up of a large fibre into numerous fine fibres (fig. 7). There is an increase of the interstitial fat in some muscles; but it is not a marked feature. Numerous muscle-spindles can be seen, and their intra-fusal fibres appear of the normal size, viz., about ·02 mm. in diameter (fig. 3).

To summarize, it may be said that the majority of the muscle-fibres present the appearance of a simple atrophy, with but little, and often no, increase of connective tissue, or of nuclei between them. Large and abnormally thick bands of fibrous tissue, and an excess of fat are, however, present in all the affected muscles. It seems possible that many of the small muscle-fibres may never have developed, as they show very little of such degenerative changes as are met with in conditions of progressive muscular atrophy in the adult. The presence of abnormally large fibres of cylindrical outline, and the occurrence of central degenerative changes, and of fission of some of the large fibres is, however, evidence that at least some of the fibres have undergone retrogressive changes similar to those which occur in both primary myopathic affections, and in the spinal muscular atrophies.

Commentary.—The clinical diagnosis of this case presented some difficulties. The marked loss of tone in the muscles, together with their weakness, suggested at first that the case was one of myatonia congenita. The onset of the weakness during the first nine months of life, and its progressive nature, however, indicated that the condition was similar to that described by Werdnig and by Hoffmann in young children under the title of "Progressive Spinal Muscular Atrophy of Infants." In support of the view that the condition was due to a spinal atrophy attention should be called to the facts: (1) That the intercostal and abdominal muscles were weak and paralysed; (2) that the paralysis of all the more proximately situated muscles was relatively greater than of the distal muscles, and (3) that the loss of tone—hypotonia—was not so great in relation to the paralysis as that which is seen in typical cases of myatonia congenita. Neither the absence of the deep reflexes nor the electrical reactions could aid in the differential diagnosis.

On the pathological side the evidence is strongly in favour of regarding the condition as primarily myelopathic. The loss and atrophy of the motor-cells of the ventral horns is very striking, and although similar changes have been described in a few cases of myopathy it has never been so severe, and in most cases no such atrophy of the spinal motor-cells is present. A similar diminution in the number and in the size of the cells has been found in the condition described by Oppenheim as myatonia congenita (Baudouin, Collier and Holmes), but it has not been nearly so severe as that which we found in this case.

It is, however, not altogether easy to confirm the view that in our case the disease is a primary myelopathic affection due to a degenerative process affecting the cells of the ventral horns, for no evidence of this degeneration in actual progress can be obtained either by the Marchi or by the Nissl method; though the latter method shows chromatolytic changes in a few cells, yet the essential feature is the *smallness* and normal appearance of such cells as are present. Even the muscle-changes cannot decide the question definitely, as it is now generally recognized that the histological differences between the primary and the secondary muscular atrophies are not so sharp and distinct as was at one time believed. Many of the changes which we have described in the muscle-fibres resemble closely those of the primary myopathies—smallness and atrophy of most of the fibres, increase in size and hypertrophy of others, central degeneration and fission of some of the hypertrophied fibres—and if we attempt to draw a distinction it must be in the relatively small amount of connective tissue that is found between the individual fibres, and in the absence or rarity of free muscle-nuclei, as compared with that which exists in dystrophic muscles. On the other hand, such features might be expected to occur if a dystrophy commenced at an exceptionally early age, when the development of the muscle-fibres is not completed or so advanced as at the age at which the disease usually sets in. It may be pointed out that the same relatively slight fibrosis of the affected muscles and rarity of free muscle-nuclei has been found in myatonia congenita, a disease which also sets in very early in life.

The whole question of the pathology of these cases of Werdnig-Hoffmann paralysis has been recently discussed by Batten in "Brain," 1911, and the cases recorded in the literature to that date are there given.

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PROGRESSIVE SPINAL MUSCULAR ATROPHY OF YOUNG CHILDREN — WERDNIG-HOFFMANN TYPE. REPORT OF A CASE, WITH PATHOLOGICAL EXAMINATION.

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AND

DOUGLAS STANLEY, M.D., M.R.C.P.

THE Werdnig-Hoffmann type of progressive muscular atrophy of young children is a disease of extreme rarity. The original cases were described by Werdnig [6] in 1891, and Hoffmann [2] in 1894, and until the year 1898 there were clinical records of eight cases only with a pathological investigation in five of them. In a recent paper Batten [1] has analysed the recorded cases since that date. There have been five other pathological examinations, one of them being on one of the cases whose clinical particulars were described before 1898. Of cases without a pathological examination, Batten admits four only as true examples of the disease. In the course of the same paper he gives details of three cases with pathological examination, and also of two other examples of the disease which came under his notice, but where he was unable to carry out any *post-mortem* investigation. This brings the total number of well-authenticated recorded instances of the disease to twenty-one.

This disease attacks children, who in nearly all cases are healthy at birth, and it not infrequently affects more than one member of a family. Muscular weakness begins at the age of a few weeks or months, and commences in the muscles of the back and pelvic and shoulder-girdles, gradually spreading from there to the distal extremities of the limbs. The intercostal muscles and those of the abdominal wall are often atrophied. The cases go progressively downhill for weeks, months, or years. The age at which death occurs has varied from a few weeks (Batten) to six years (Werdnig, Thomson and Bruce [5]), and the fatal termination is not infrequently due to bronchopneumonia. *Post-mortem*, the constant pathological change is an atrophy of the anterior horn cells.

Case.—C. P., a boy, aged 3, was the fifth child of a family of six children, all of whom were born at full term, and three of whom died in infancy from "chest and fits." The sixth child, aged 18 months, can walk well. There were no miscarriages. Until 10 months old the patient was a "normal" child; he then had an attack of bronchitis, after which wasting became apparent. At a year he could move his legs quite well, also his arms at the elbow, but was unable to lift the arms above the shoulder. In the legs wasting was first observed in the upper part of the thigh. He was never able to sit up alone, although when propped up he was able to maintain that position for some time. He has been able to roll himself over, but has never been able to pull himself along the ground, to crawl, or to stand. For the twelve months before admission to hospital he has been unable to hold his head erect, although well able to do so before; this loss of power has been quite gradual, and even up to the date of his admission into hospital he was able on occasions to "roll his head" up. During this time he has also developed a deformity of the chest. Since the first attack of bronchitis he has had frequent similar attacks. For two years his voice has been getting weaker, although improving a little, with improvement in the chest condition. At the time he came to the Out-patient Department of the Children's Hospital, Birmingham, he was said to be putting on weight, and to be stronger than he had been for some time previously. In May, 1911, he was admitted.

On admission he was noticed to be a very intelligent boy, who talked quite well. He was markedly wasted, weighing 19 lb. He lay comfortably on his back in bed, and could be freely moved about without pain; he was unable to raise himself into a sitting position, but when propped up he could maintain that position for a little time. He was also unable to hold his head erect, and as a result his head flopped about, first on one shoulder and then on the other.

The ocular nerves appeared normal, the pupils were active and equal. There was no paralysis of the facial muscles, tongue, or palate, and swallowing was normal.

His arms were thin, flaccid, and assumed a position of pronation. The muscles of the shoulder-girdle were most affected, being nearly completely paralysed. Supination was impossible, and there was well-marked wrist-drop. He could hold objects in his hand, and with great difficulty convey a small spoon to his mouth. All movements of the fingers could be carried out, but in a very weak manner. The small muscles of the hand did not appear to be wasted. The fingers were long and thin, and their extremities were bulbous. The hands generally assumed the following position: Wrist-drop, flexion at the metacarpophalangeal joints, and extension of the interphalangeal joints of the second to fifth digit; the metacarpal of the thumb slightly opposed to the palm with hyper-extension at both metacarpo- and inter-phalangeal joints. In grasping objects the first and second digits were usually employed, and these with a slow, seizing action, not unlike the way in which a lobster uses his large claws in seizing objects. This curious "athetoid" movement and the amount of overaction accompanying it has been pointed out by Batten. The lower limbs were very thin, the wasting being most apparent above the knee. Both limbs were adducted, the left to a greater degree than the right, internally rotated, and slightly flexed at both hip- and knee-joints. The right foot was in the position of a talipes equino-varus, and the left foot lay on its inner side with the sole everted. The legs could not be extended fully at the knee- or hip-joints and the adductors showed a considerable amount of contracture; apart from this the flaccidity of the limbs was very marked, and passive movements could be freely performed. Of voluntary movements he was only able to flex and extend his toes, and to flex and extend the ankle. These movements were rather weak, especially that of extension of the toes, and therefore the ankle was kept in an extended position. The feet did not appear to be wasted.

Both hands and feet showed a considerable degree of hypotonia, but the most striking feature was the flaccid paralysis of arms and legs. The abdominal muscles were very atrophic, the abdomen being ballooned, and many fæcal masses could be felt through the abdominal wall. Respiration was entirely diaphragmatic, and the intercostal, together with the abdominal, muscles appeared to be completely paralysed. The thorax showed a very well-marked deformity of the "Trichterbrust" variety. The back muscles were weak and wasted. When the child was propped up, there was a well-marked lateral curvature in the lower dorsal and lumbar regions, having its convexity towards the left.

The knee-, ankle-, and arm-jerks, and the abdominal reflexes were all absent. Plantar reflexes were indefinite in type, and the organic reflexes were all normal. No alteration in sensation was found. Electrical examination showed a marked diminution of excitability and a slight reaction of degeneration. Lumbar puncture gave a clear fluid which showed a few lymphocytes, but hardly more than normal.

He remained in hospital until his death from bronchopneumonia in October, 1911. During this time the amount of paralysis did not appear to increase in the arms, and sometimes he appeared to have more strength in his neck muscles than at others. Paralysis in the lower limbs rather increased, and a day or so before his death the only movements possible were very feeble extension and flexion of the toes. Movement at the ankle-joint appeared to be impossible, and a condition of slight pes cavus had developed.

Autopsy.—This was performed twenty-four hours after death. The limbs retained the positions described above, they were covered with a fair amount of subcutaneous fat which made the muscular wasting even more marked than had been expected. Of the muscles examined the erector spinæ, glutei, latissimus dorsi, rhomboids and trapezius (particularly the lower half) were all small and atrophied. The sternomastoid and the pectoralis major were also very pale and atrophic, but not to the same degree throughout, the sternal part of the sternomastoid and the upper part of the pectoralis major being less affected than the other parts of the muscles. The pectoralis minor was also very wasted, and the intercostal muscles together with those of the abdominal wall had almost completely disappeared; the few fibres which remained were very pale. The deltoid was pale and wasted to an extreme degree. The biceps and coracobrachialis were very wasted, but still contained a fair amount of apparently healthy fibres. The psoas and iliacus muscles, on the other hand, were extremely pale and atrophic. The diaphragm in contrast to the other muscles was of a good colour, and did not show any atrophy to the naked eye. All these changes appeared to be present in the same degree on both sides of the body.

There was very extensive bilateral bronchopneumonia. None of the other viscera showed any abnormality except that the intestines appeared to be thin walled.

The brain and cord showed no changes to the naked eye, but the anterior nerve-roots were smaller than normal.

Microscopical examination.—The muscles examined microscopically were the biceps, psoas and diaphragm. These were embedded in celloidin, and examined by Van Gieson's and Marchi methods. Paraffin sections of the intestine stained by hæmatoxylin and Van Gieson were also examined.

The biceps and psoas by Van Gieson's method show marked changes. (*See* figs. 1, 2, 3 and 4.) There is a considerable increase in the amount of fibrous tissue, which is in parts distinctly more cellular than usual; in places it forms dense bands separating the various muscle-bundles. The muscle-fibres show many variations, and these are not localized to any one particular part of the section, but seem to be distributed more or less through the whole muscle, so that bundles of apparently normal fibres are seen in close proximity with those showing very marked changes. The more normal fibres occupy a somewhat larger proportion of the muscle than the altered ones. The normal fibres seem to have rather more nuclei than the normal, and a few show central nuclei. Some of the fibres are much larger than normal, and have lost their polygonal outline, becoming rounded; others, although larger than normal, retain their polygonal outline. By far the greater proportion of the altered fibres are, however, smaller than the normal, some being extremely small and on the point of complete atrophy. These small fibres in cross section measure ·01 mm. and less, and show an enormous increase in the number of nuclei, so that parts of the section appear to be swarming with nuclei. On cross-section at first sight these nuclei rather appear to belong to fibroblastic cells. Some of them are, since fine fibrous tissue can be traced in between some of these fibres; but longitudinal section of the muscle shows that nearly all these nuclei belong to minute muscle-fibres, many of which exhibit very well-marked striation. These minute fibres seem to be formed by the splitting of larger fibres, and at the point of cleavage proliferation of the nuclei occurs. Many of these fine fibres seem to pass imperceptibly into fibrous tissue, and in cross-section some of them are seen embedded in fairly dense fibrous tissue.

Striation is on the whole well preserved. Some fibres seem to have lost their striation in whole or part, but on the other hand many of the small fibres retain their striation until their complete disappearance.

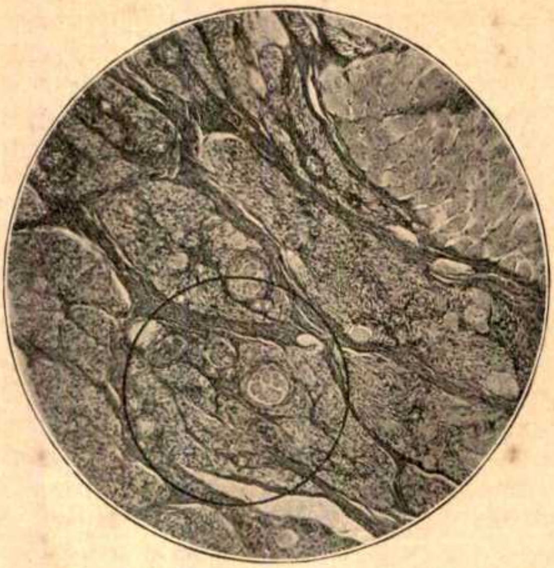

FIG. 1.—Cross section of biceps (× 80 diams.), stained with hæmatoxylin and Van Gieson's method. In the upper right quadrant are normal fibres. The majority of fibres are of the atrophic variety. Several muscle spindles are present and there is much fibrosis. The area enclosed by the ring forms fig. 2.

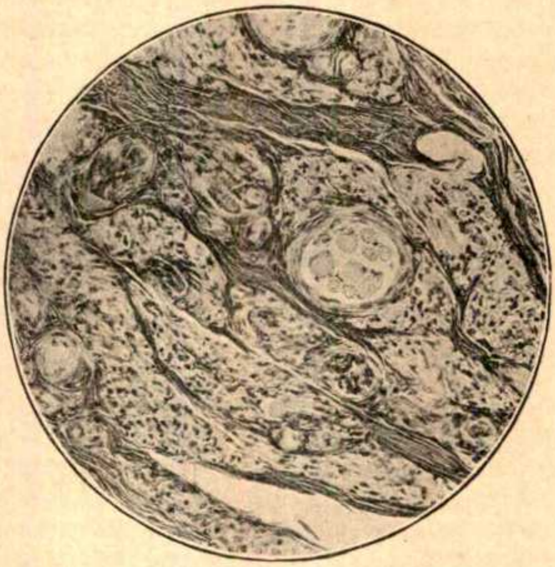

FIG. 2.—Higher magnification (× 250 diams.) of the part of fig. 1, enclosed by the ring, showing the characters of the atrophic muscle-fibres and of the fibrous tissue. Close to the centre is a normal muscle spindle. The atrophic fibres measure ·01 mm. and less in cross-section, and the fibres in the muscle spindle ·025 mm. and ·02 mm.

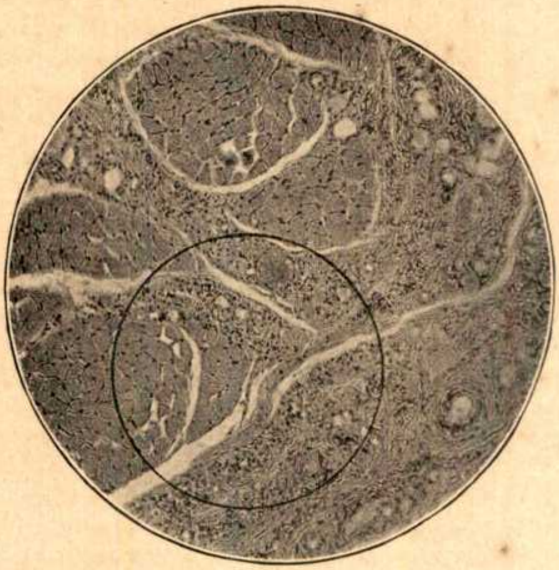

FIG. 3.—Cross-section of psoas (× 80 diams.) stained with hæmatoxylin and Van Gieson's method, showing fibrosis and close proximity of atrophic and more normal muscle-fibres. The area enclosed by ring forms fig. 4.

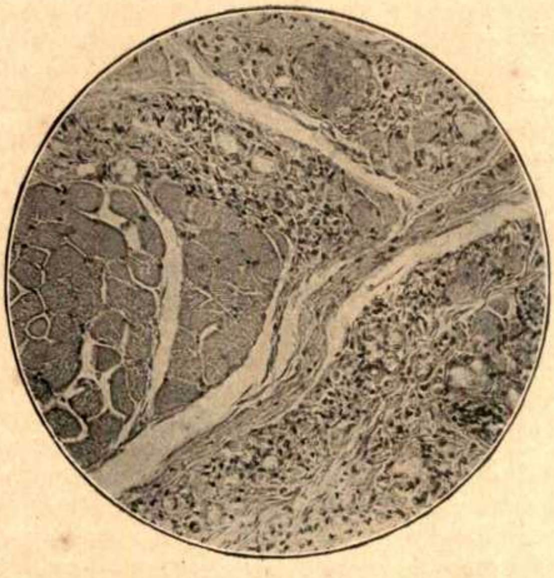

FIG. 4.—Higher magnification (× 250 diams.) of part of fig. 3 enclosed by the ring, showing variations in size of the atrophic fibres and the great increase in the number of nuclei.

Muscle-spindles show a normal structure; they are very well seen, and in the biceps particularly they are present in good numbers. They show no change even when situated in the middle of muscle-bundles of fine muscle-fibres (*see* figs. 1 and 2). The fibres in the spindle measure ·025 mm. and ·02 mm. in cross section.

There is a certain amount of increase in the interstitial fat. The intramuscular nerves stain quite well, but there appears to be an increase in the amount of endoneurium. The blood-vessels do not show any marked changes.

By the Marchi method there is seen to be a considerable increase in the amount of interstitial fat. A large number of the muscle-fibres show no change, but others show a well-marked fatty degeneration. This degeneration is a true one, being distributed throughout the whole fibre and not consisting in fat droplets deposited in the neighbourhood of the nucleus. The fatty change is present chiefly in the normal-sized fibres, but it is also seen in some of the atrophic ones, and in some of the small muscular fibres of the muscle spindles.

These changes are all rather more pronounced in the psoas than in the biceps. The diaphragm is almost normal, but pathological changes have commenced, for there is a slight increase in the amount of fibrous tissue, and a few of the small multi-nucleated muscle-fibres are present. The involuntary muscles of the intestines appear quite normal.

The spinal cord was examined by the following methods: Weigert-Pal, Marchi, Nissl and Van Gieson. In the Weigert-Pal sections the whole of the anterolateral part of the cord stains more lightly than the posterior columns but it is not possible to pick out any particular tract as more definitely affected than the others. The fibres of the anterior root are seen to be much fewer than those of the posterior root, the anterior root being strikingly smaller than the posterior root.

By the Marchi method no recent degeneration was found in the cord, peripheral nerves, posterior or anterior nerve-root, or posterior root ganglia.

The sections stained by Nissl's method showed a most striking diminution in number of the cells of the anterior horn. This diminution affects all parts of the cord, and in the dorsal region contrasts greatly with the cells of Clarke's column. The amount of this diminution is shown by comparing fig. 5—a photograph of the anterior horn of one of the lower lumbar segments—with fig. 6, a photograph of the anterior horn in the same region in a normal child. Fully two-thirds of the cells have disappeared, and the figures also show that the majority of those cells which do remain are considerably smaller than normal. Serial sections of the cervical and lumbar enlargements were examined. It is a rarity to find in these sections cells of the normal size in the anterior cornua, indeed many seem just on the point of complete disappearance. The small cells frequently show an eccentric nucleus, some diminution in the amount of chromatin, and few or no processes. A few cells were found which showed complete chromatolysis; of these the larger number were in the lumbar region, a fact which in all probability fits in with the

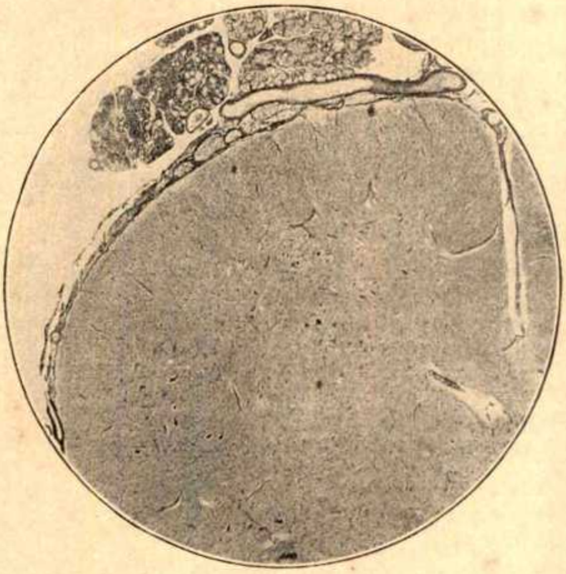

FIG. 5.—Section of anterior horn and anterior nerve root from lower lumbar region stained with hæmatoxylin and Van Gieson's method, showing the great diminution in number and size of the cells of the anterior horn, also the fibrosis and atrophy of the anterior nerve root. Compare with fig. 6.

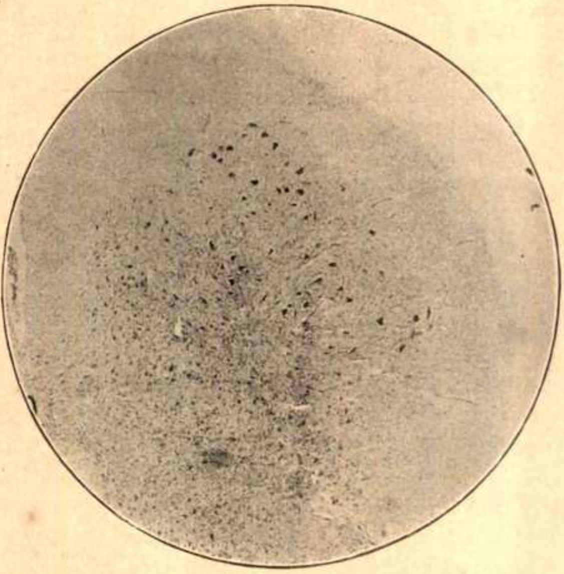

FIG. 6.—Section of anterior horn in the lower lumbar region of a normal child, stained with hæmatoxylin and Van Gieson's method, for comparison with fig. 5.

clinical observation that the increase of paralysis during the last few weeks of life was most apparent in the lower limbs.

The sections stained by Van Gieson's method also showed very well the diminution and atrophy of the anterior cornual cells; in addition they show that there is no overgrowth of the neuroglia in any part of the cord, and that the vessels are normal. The meninges show no change. The size of the anterior roots has been already commented on (*see* fig. 5). They show a considerable increase of fibrous tissue, which contains many fibroblasts, and many of the nerve-fibres take the stain badly. This increase of fibrous tissue has been stated to occur in the intermuscular nerves; it was also found in some of the branches of the brachial plexus examined by this method, but the amount of fibrous tissue was less than that found in the anterior nerve-roots.

The posterior roots and their ganglia were normal by all the methods of examination employed, and so was the medulla.

These pathological findings agree well with those described in the other recorded *post-mortem* examinations on the disease, viz.—great diminution in size and number of the cells of the anterior horn, atrophy of the anterior nerve-roots, fibrosis and atrophy with lipomatosis of the muscles. These findings, while agreeing closely with one of the three *post-mortems* recorded by Batten in his paper, differ from the two younger cases, in the absence of any distinct change by the Marchi method in the anterior roots—intra- and extra-medullary—and in the diminution in the number of cells. In this paper Batten advanced the view that the presence of these Marchi changes in the younger fatal cases, and their absence in the older ones, the presence of little chromatolysis in the younger, and increased chromatolysis and later atrophy of the anterior cornual cells in the older cases, was really due to the severity and duration of the disease; that at a later stage the products of degeneration as shown by the Marchi method became absorbed, whilst the chromatolysis and atrophy of the cells as shown by the Nissl method became more marked. Such an explanation seems to be in all probability the correct one. The slight change observable in our case in the Weigert-Pal sections has also been noticed in other cases (Batten, Werdnig [6], Hoffmann [3]).

REEFRENCES.

[1] BATTEN. *Brain*, 1910-1911, vol. xxxiii, p. 433.
[2] HOFFMANN. *Deutsche Zeitschr. f. Nervenheilk.*, 1893, Bd. iii, S, 427.
[3] *Idem. Ibid.*, 1897, Bd. ix, S. 264.
[4] *Idem. Ibid.*, 1895, Bd. vi, S. 153.
[5] THOMSON and BRUCE. *Edin. Hosp. Reports*, 1893, vol. i, p, 361.
[6] WERDNIG. *Arch. f. Psychiat.*, 1891, Bd. xxii, S. 437.

PUBLICATIONS RECENTLY RECEIVED.

[*Notes on a book under this heading do not preclude a subsequent review.*]

La Fonction Cérébelleuse. Par le Dr. ANDRÉ-THOMAS. Pp. 330. Avec 89 figures dans le texte. Paris: Doin et Fils, 1911.

This excellent little book is an attempt to set out clearly the main facts which have emerged from recent work on the structure and functions of the cerebellum. The anatomy is dealt with rather shortly, but the experimental results are treated fully and are followed by a description of the symptoms of cerebellar disease. The last half of the book is devoted to discussion of the significance of these phenomena, and this useful summary is furnished with a good index.

The Wassermann Sero-Diagnosis of Syphilis in its Application to Psychiatry, Nervous and Mental Disease. Monograph No. 5. By Dr. FÉLIX PLANT. Authorized translation by Smith Ely Jelliffe, M.D., and Louis Casamajor, M.D. Pp. 188. New York: Journal of Nervous and Mental Disease Publishing Company, 1911.

This monograph is an unusually interesting account by one of Professor Wassermann's pupils and fellow-workers of the results obtained with this reaction in cases of cerebral syphilis and parasyphilis. The author begins with a short historical introduction, and, after a chapter devoted to technique, discusses the clinical specificity of the Wassermann reaction. General paralysis, cerebral syphilis, tabo-paresis, and feeble-mindedness on an hereditary syphilitic basis are all discussed quietly and judicially. The results arrived at correspond closely with those enunciated by Neisser and Nonne in Germany and Mott in this country.

Bericht über die Leistungen auf dem Gebiete der Anatomie des Centralnervensystems, 1909 und 1910. Von L. EDINGER und A. WALLENBERG. Bonn: Marcus und Weber, 1912.

This, the seventeenth biennial report on the anatomy of the nervous system which Edinger has edited, is considerably larger than its forerunners, though the number of articles actually reviewed is smaller; this allows a welcome increase in the space devoted to some of the more important. The work has also been more divided up among men who are recognized authorities in the subjects they have undertaken. Brodmann, for instance, deals with the cerebral cortex, H. Vogt with the forebrain, and Röthig has been largely responsible for the sections on comparative anatomy.

As the authors remark, the period included in their review has not been distinguished by any prominent discovery in the anatomy or histology of the nervous system; the most notable feature has been the extending interest in comparative anatomy. The most interesting sections in the report are those on the histology of [illegible] cell and fibre, which contain references to over 200 [illegible] and hypophysis, and, finally, the long chapter [illegible]

The report equals its predecessors in the fair, judicious and critical spirit in which it is written, and it is indispensable to all working at, or interested in, the anatomy and morphology of the nervous system.

Die Tabes der Frauen. Von K. Mendel und E. Tobias. Berlin: Karger, 1912.

This monograph is based on the study and analysis of 151 cases of tabes in women. It is chiefly statistical and brings out many points of importance, especially in comparison with tabes in the male sex. However, we think the authors' plea is scarcely made out that its publication is justified by the fact that many of the symptoms of tabes appear differently in the male and female, and that in the latter the disease often bears a special character, One of the most interesting points is the large percentage of cases in which evidence of syphilitic infection can be ascertained by careful examination. Wassermann's reaction too, was positive in 83 per cent. of the cases examined, which is definitely higher than in the male cases investigated during the same period.

Feeble-mindedness in Children of School Age. By C. Paget Lapage, M.D. With an appendix on treatment and training, by Mary Dendy, M.A. Pp. 359. Manchester: University Press, 1911.

This book is a simply written account of the natural history of the feeble-minded, more for the practitioner and social worker than for specialists. The relation of the feeble-minded to the State and local authorities is clearly set out and the anti-social danger insisted upon. Various forms of feeble-mindedness are described and illustrated with photographs. Finally, there is an interesting and practical appendix on diet, clothing, and methods of education.

Diseases of the Nervous System. By Judson S. Bury, M.D., F.R.C.P. Pp. 778. Manchester: University Press, 1912.

A most useful text-book for the senior student and practitioner. The descriptions are short and to the point, and all the recent advances in clinical diagnosis are included. The illustrations are clear and the coloured plates excellent.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I. to XXIII. inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

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EDITOR.

[NOVEMBER, 1912.]

BRAIN.

PART II., VOL. 35.

Original Articles and Clinical Cases.

SOME OBSERVATIONS ON THE GROWTH AND SURVIVAL-PERIOD OF INTRACRANIAL TUMOURS, BASED ON THE RECORDS OF 500 CASES, WITH SPECIAL REFERENCE TO THE PATHOLOGY OF THE GLIOMATA.[1]

BY HOWARD H. TOOTH, M.D.

THE following observations form part of a general inquiry into the history, progress, treatment, fate, and, in many cases, the *post-mortem* findings of persons suffering from intracranial new growths who have come under observation at the National Hospital during the period of ten years, 1902-1911 inclusive.

I have here to make grateful acknowledgment of the permission of my colleagues to use the notes of their cases, and the ready help given me on all occasions, especially in the difficult matter of tracing the after-history of patients. As the numbers are large, and the notes in most cases voluminous, many being models of medical note-taking, it may not be out of place to say a word upon the method employed, especially as the value of some of the tables submitted depends entirely upon the accuracy of interpretation of the recorded clinical details, and the information received from the patients themselves, both of which constitute the main difficulty in an inquiry of this nature.

A careful abstract of the clinical features has been made upon a card under an index number, a running card-index of clinical points being made at the same time. This card also receives all other information that can be obtained, namely: (1) An account of operation, and further course of the case; (2) an abstract of the *post-mortem* examination—no small part of the task, which has been undertaken by my colleague

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[1] Presidential Address (Section of Neurology), Royal Society of Medicine.

Dr. Howell, then pathologist, to whom I offer my best thanks; (3) an examination of the microscopical appearances; (4) all patients who have left the hospital have been written to—a circular letter with a short series of easily answered but sufficiently searching questions on the fly-sheet, and on the whole the answers have been intelligent, and of use in forming an opinion of the present state; 346 of these letters have been sent out, and 177 answers returned from patients or their friends; the remainder have not been answered, or the letters have been returned through the post. In forming tables of results, therefore, it has been necessary to assign a column of "No reply."

My junior colleagues, who have in the last ten years served on the Resident Staff, have kept in touch with some of these "No reply" cases to fairly recent dates, so this group affords some information of value. These facts are entered upon the cards.

During the ten years there have been in hospital 566 cases diagnosed as new growths, or as gummata. The gummata, 40 in all, have been rejected as requiring separate consideration. On close consideration, also, 26 cases have been eliminated for various reasons, not the least being the absence of optic neuritis. These rejections leave 500 cases of practically certain intracranial tumour, and it is from these that the facts and conclusions which follow have been gathered.

Table I presents the distribution of these tumours according to the regions of the brain involved. The larger number have been verified by operation or *post-mortem* examination. Many, of course, have been subjected to neither of these tests, but from the clinical details one may have little hesitation in accepting the diagnosis as correct, and these have been used for the estimation of the period of growth of tumours, whether still alive or since dead, without verification *post-mortem*.

To show how difficult is this question of rejecting or retaining cases in the absence of verification, I must refer to two cases amongst the rejections. The first, a woman, aged 43 (Dr. Beevor), who had suffered nineteen years before from severe fits, ten years torticollis, and frequent faints, five months posterior headache, five weeks a Jacksonian convulsion, left hand and arm preceded by an aura in the same situation. On admission she presented the picture of right precentral tumour: mental levity, intense optic neuritis, blurred vision, left hemiplegia, exaggerated left deep reflexes. The brain was explored by Sir V. Horsley over the region indicated, and nothing was found. There was much bulging afterwards, but the neuritis subsided to pallor, and she became almost blind. Six weeks after operation she had a series of fits, beginning with purposive movements of the right arm, becoming clonic later, and, as the fit subsided, similar movements on the left side, followed by coma. Nearly five months after she became alternately stuporose and noisy, again a series of right-sided fits, coma, and death from respiratory failure. *Post-mortem* no tumour was found, but great general rise of intracranial pressure, so as to force the posterior part of

TABLE I.—REGIONAL CLASSIFICATION OF CASES OF ALL TUMOURS, WHETHER VERIFIED OR NOT.

Region	Sex		Total	Per cent.	
	M.	F.			
(1) Frontal	60	40	100	21·7	Fore-brain : 239. 52 per cent.
(2) Central pre- and post. Parietal	43	20	63	13·7	
(3) Temporo-sphenoidal ...	24	25	49	10·6	
(4) Occipital	8	6	14	3·0	
(5) Corona radiata; corpus callosum, &c.	4	6	10	2·1	
(6) Lateral ventricle	2	1	3	0·6	
(7) Pituitary	10	4	14	3·0	
(8) Optic thalamus	4	2	6	1·3	
(9) Mesencephalon	18	8	26	5·2	Mid-brain : 30. 6·5 per cent.
(10) Pineal	4	—	4	0·8	
(11) Choroid plexus; III and IV ventricles	4	1	5	1·0	
(12) Cerebellum	44	33	77	16·7	Cerebellum and pons : 160. 34·2 per cent.
(13) Extra-cerebellar	19	21	40	8·7	
(14) Pons	19	24	43	9·3	
(15) Medulla	—	1	1	0·2	
(16) Base	1	3	4	0·8	
Total	264	195	459		
(17) Not localized	24	17	41		
Grand total	288	212	500		

the cerebellar lobes down into the foramen magnum—so-called pressure-cone. Dr. E. F. Buzzard made some 500 sections of the brain, and failed to find any cause for the symptoms. This may not be a rare case—in fact, there have been three similar cases—but if the *post-mortem* findings were not to hand it would have come into my table as a tumour of the Rolandic area.

The second case was of optic neuritis with swelling without localizing symptoms. This was rejected as a case of family optic neuritis. Her sister had been in hospital one year before with the same symptoms, and eventually quite recovered. Both had suffered from severe headache, parietal and frontal, and both had been diagnosed as tumor cerebri. Again, there may be many such.

Therefore the group "Not localized" has little value, and is placed by itself in this table. It has been used in Table II, age-incidence, but in the other tables in which it occurs it is taken by itself on its own merits.

There can be little doubt that a fair number in this group are Frontal and Temporo-sphenoidal cases, latent or of slow growth; some may be deeply seated subcortical growths in the Corona radiata or ventricles, regions of indefinite symptomatology. It will be seen that the two most vulnerable regions are the Frontal and the Cerebellum. But if we take the Frontal and Parietal together, which, considering the great tendency to overlapping, is a reasonable thing to do, and for the same reason we link together the Cerebellum and Pons, it is remarkable how closely in the respect of vulnerability these two antipodal regions correspond—i.e., Fronto-parietal 163 cases, Ponto-cerebellar 160—making together more than half the total of all growths, whether verified or not, for all regions.

In the Fore-brain, which includes the first six regions in Table I, and which claims 52 per cent. of the whole number, the Frontal group heads the list with 100 cases, 21·7 per cent. of the total, and 41·8 per cent. of the Fore-brain. We have much exact knowledge both of localization, and of the characters, of the growths of this region, by reason of the fact that operations have been performed in 74 per cent. of the cases. The Central group is smaller, 63, but owing to the comparatively clear and definite symptomatology of the motor region, operations have been performed in a yet larger percentage of cases—i.e., 52 out of 63, or 82·5 per cent.

Of tumours of the Temporo-sphenoidal region we have a fair number, 49. The diagnosis of lesions of this region is among the most difficult,

TABLE II.—AGE AT APPEARANCE OF FIRST SYMPTOM FOR ALL GROWTHS, VERIFIED OR NOT.

Region	Sex		Total	1—20 years		21—30 years		31—40 years		41—50 years		51—60 years		61—70 years	
	M.	F.		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
(1) Frontal	60	40	100	9	9·0	30	30·0	39	39·0	14	14·0	7	7·0	1	1·0
(2) Central (parietal)	43	20	63	9	14·2	12	19·0	19	30·0	16	25·3	6	9·5	1	1·5
(3) Temporo-sphenoidal	24	25	49	10	20·4	14	28·5	18	36·7	5	10·2	2	4·0	—	—
(4) Occipital	8	6	14	2	14·2	4	28·5	1	7·1	3	21·4	4	28·5	—	—
(5) Corona radiata, corpus callos., &c.	4	6	10	1	10·0	3	30·0	—	—	2	20·0	4	40·0	—	—
(6) Lateral ventricle	2	1	3	1	33·3	—	—	2	66·6	—	—	—	—	—	—
(7) Pituitary	10	4	14	2	14·2	6	42·8	4	28·5	2	14·2	—	—	—	—
(8) Optic thalamus	4	2	6	1	16·6	1	16·6	2	33·3	2	33·3	—	—	—	—
(9) Mesencephalon	18	8	26	12	46·1	9	34·6	3	11·5	1	3·8	1	3·8	—	—
(10) Pineal	4	—	4	1	25·0	2	50·0	—	—	1	25·0	—	—	—	—
(11) Choroid plexus, III and IV ventricles	4	1	5	1	20·0	2	40·0	—	—	2	40·0	—	—	—	—
(12) Cerebellum	44	33	77	47	61·0	14	18·1	10	14·2	3	3·8	3	3·8	—	—
(13) Extra-cerebellar	19	21	40	5	12·5	7	17·5	19	47·5	6	15·0	2	5·0	1	2·5
(14) Pons	19	24	43	23	53·4	7	16·2	8	18·3	5	11·6	—	—	—	—
(15) Medulla	—	1	1	1	—	—	—	—	—	—	—	—	—	—	—
(16) Base	1	3	4	1	25·0	—	—	—	—	1	25·0	2	50·0	—	—
(17) Not localized	24	17	41	13	31·7	12	29·2	12	29·2	2	4·8	2	4·8	—	—
Totals	288	212	500	139	—	123	—	137	—	65	—	33	—	3	—

yet a large number, 32, or 65·1 per cent., have come to operation and with a lower mortality than in the two preceding groups. The occipital group is much smaller, only 14, and as the localization is not difficult owing to the rather sharp symptomatology referable to the optic radiations and angular gyrus, it may be inferred that tumours in this region are comparatively rare. Operations have been performed in seven cases—i.e., 87·7 per cent. The Mid-brain group includes 26 cases, to which may be added the Pineal cases, making together 30, or 6·5 per cent. of the whole. The diagnosis of these lesions has been made more practicable by the work of Head and Holmes, and probably in the future the percentage of this group will be higher, but I fear surgery offers little hope of help in dealing with such cases.

The Cerebellum proper offers 77 cases, 16·7 of the whole, and as the clinical indications are fairly well marked, this is probably a true figure; 36, or 46·7 per cent., have been verified by operation.

Of the Extra-cerebellar group, 5 are Gliomata and 13 Fibrogliomata, and therefore primary in the Cerebellum, but as their line of growth was almost entirely in the lateral recess, I have included them in this group. There were 40 in all, and 32, or 80 per cent., came to operation.

Of tumours of the Pons there were 43, or 9·3 per cent.; they require no comment in this connexion.

Growths of the Medulla must be very rare. I find record of only 1, an infiltrating Glioma.

Table II: Age at appearance of first symptom.—This, of course, is not necessarily a true indication of the age of the tumour, which may have existed in a latent state for any length of time. The table requires little comment. Its value is regional only. Of tumours of the Fore-brain generally, 142, or 59·4 per cent., made their first manifestation between the ages of 21-40; 32 only, or 13·4 per cent., between 1-20; 63, or 26·7 per cent., between 41-60; and only two in the last decennium, one of which was strictly 72.

Of the Mid-brain group 21, or 80·7 per cent., appeared first between ages 1-30, 12 of these falling between 1-20. Of the Ponto-cerebellar tumours (excluding Extra-cerebellar; in 70 cases, or 58·3 per cent., symptoms appeared first between 1-20, 21, or 17·3 per cent., between 21-30, 18, or 15 per cent., between 31-40, and only 8, or 6·6 per cent., between ages 41-50.

But the Extra-cerebellar group more nearly resembles in age-incidence the Fore-brain tumours, in that the larger number, 19, or 47·5 per cent., fall between ages 31-40.

TABLE III.—AGE AT APPEARANCE OF FIRST SYMPTOMS FOR GROWTHS OF WHICH THE NATURE HAS BEEN VERIFIED ON OPERATION OR POST-MORTEM.

Nature of growth	1—20 YEARS				21—30 YEARS				31—40 YEARS				41—50 YEARS				51—60 YEARS				61—70 YEARS				Total	Per cent.
	M.	F.	Total	Per cent.	M.	F.	Total	Per cent.	M	F.	Total	Per cent.	M.	F.	Total	Per cent.	M.	F.	Total	Per cent.	M.	F.	Total	Per cent.		
Glioma ...	9	16	25	19·6	25	12	37	29·1	25	7	32	25·1	14	5	19	14·9	8	5	13	10·2	—	1	1	0·7	127	49·2
Fibroglioma...	—	2	2	13·3	—	4	4	26·6	2	4	6	40·0	1	2	3	20·0	—	—	—	—	—	—	—	—	15	5·8
Fibroma ...	2	2	4	30·7	—	—	—	—	7	2	9	69·2	—	—	—	—	—	—	—	—	—	—	—	—	13	5·0
Endothelioma	4	2	6	16·2	2	2	4	10·8	8	8	16	43·2	7	2	9	24·3	1	1	2	5·3	—	—	—	—	37	14·3
Sarcoma ...	3	—	3	14·2	5	—	5	23·8	5	1	6	28·5	3	3	6	28·5	—	1	1	4·7	—	—	—	—	21	8·1
Carcinoma ...	—	—	—	—	—	—	—	—	3	—	3	20·0	3	3	6	40·0	3	2	5	33·3	1	—	1	6·6	15	5·8
Tuberculoma	4	5	9	64·2	2	2	4	28·5	1	—	1	7·1	—	—	—	—	—	—	—	—	—	—	—	—	14	5·4
Cyst, simple...	3	—	3	60·0	2	—	2	40·0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5	1·9
Papilloma ...	—	—	—	—	1	—	1	33·3	—	—	—	—	1	1	2	66·6	—	—	—	—	—	—	—	—	3	1·1
Cholesteatoma	—	—	—	—	—	1	1	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	2	0·7
Pituitary ...	—	—	—	—	1	—	1	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	2	0·7
Pineal ...	1	—	1	—	2	—	2	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—	—	—	4	1·5
Totals ...	26	27	53	20·5	40	21	61	23·6	53	22	75	29·0	30	16	46	17·8	12	9	21	8·1	1	1	2	0·7	258	—

To sum up briefly, it would appear that tumours of the Fore-brain tend to appear more frequently in middle age, but no age is exempt. Those of the Mid-brain, on the other hand, appear first predominantly in the early or adolescent period, and the same may be said of the Cerebellum and Pons; comparatively few occur after 30.

Table III has perhaps more interest than the last, and though the figures are smaller they include verified cases, and are therefore of more value. The Gliomata come first, 127, or 49·2 per cent., and it is seen that the numerical age-incidence for each decennium to 50 is fairly similar, but the largest number falls between 21-40. The Fibrogliomata are few, but they conform in this respect with the last.

The same may be said of the Endotheliomata: the largest number, 16, or 43·2 per cent., of the group falling between 31-40.

The Sarcomata show practically the same age-incidence.

Carcinomata, as might be expected, appear in later periods, 31-60, but they are few.

Tuberculomata also are few, 14 only; of these 9 appear between 1-20, and only 1 between 30-40. The remaining growths are too few to base any conclusions upon.

Heredity.—In the records of cases heredity receives due attention. The class of patients at this hospital, generally speaking, is perhaps somewhat above that of general hospitals, so that diseases so striking as tumour of the brain, or cancer, might be expected not to be overlooked by the patient or friends. Yet among the 500 cases I find a cancerous heredity in no more than 37 cases, or 7·2 per cent. Of these 13 were in the father and 2 others on his side, 15 in the mother and 2 others on her side, 1 brother, 3 sisters, 1 aunt. In 10 the growth in the patient was Glioma, in 2 Fibroglioma, in 4 Fibroma, in 2 Endothelioma, and in 1 Tuberculoma. In 17 the nature of the growth was not known.

In no case is there any family history of tumor cerebri. We may assume, then, that heredity is a negligible factor.

Table IV: Regional incidence of growths verified on operation or *post-mortem* examination.—The accuracy of this table depends upon the correct interpretation of the microscopical appearances of the section preserved, and some of them are so puzzling that their proper place in this table is almost a matter of opinion. With this reservation the table may be considered for practical purposes a true statement.

Glioma.—It is evident that of all growths the Glioma is the largest in number and the most universal in its incidence. Of the total 258

TABLE IV.—REGIONAL INCIDENCE OF GROWTHS VERIFIED ON OPERATION OR POST-MORTEM.

Region	No. of growths for each region	GLIOMA		FIBROGLIOMA		FIBROMA		ENDO-THELIOMA		SARCOMA		CARCINOMA		TUBERCU-LOMA		CYST		PAPILLOMA		CHOLESTEA-TOMA		PITUITARY		PINEAL ADENOMA	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent
(1) Frontal ...	68	38	55·8	—	—	—	—	21	30·8	4	5·8	4	5·8	1	1·4	—	—	—	—	—	—	—	—	—	—
(2) Central ...	43	25	58·1	—	—	—	—	10	23·2	3	6·9	5	11·6	—	—	—	—	—	—	—	—	—	—	—	—
(3) Temporo-sphenoidal	27	17	62·9	—	—	—	—	4	14·8	2	7·4	2	7·4	2	7·4	—	—	—	—	—	—	—	—	—	—
(4) Occipital ...	6	4	66·6	—	—	—	—	—	—	1	16·6	1	16·6	—	—	—	—	—	—	—	—	—	—	—	—
(5) Corona radiata, corp. callos.,&c.	8	6	75·0	—	—	—	—	—	—	1	26·5	1	26·5	—	—	—	—	—	—	—	—	—	—	—	—
(6) Lateral ventricle	3	1	33·3	—	—	—	—	—	—	2	66·6	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(7) Pituitary ...	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	—	—	—
(8) Optic thalamus	3	1	33·3	—	—	—	—	—	—	2	66·6	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(9) Mesencephalon	8	4	50·0	—	—	—	—	—	—	1	12·5	—	—	2	25·0	1	12·5	—	—	—	—	—	—	—	—
(10) Pineal ...	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4	—
(11) Choroid plexus, III and IV ventricles	4	—	—	—	—	—	—	—	—	1	25·0	—	—	—	—	—	—	3	75·0	—	—	—	—	—	—
(12) Cerebellum ...	34	18	52·9	—	—	1	2·9	1	2·9	3	8·8	1	2·9	6	17·6	4	11·7	—	—	—	—	—	—	—	—
(13) Extra-cerebellar	32	5	16·3	13	40·6	11	34·3	1	3·1	—	—	—	—	—	—	—	—	—	—	2	6·2	—	—	—	—
(14) Pons	12	7	58·3	1	8·3	1	8·3	—	—	—	—	—	—	3	24·9	—	—	—	—	—	—	—	—	—	—
(15) Medulla ...	1	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(16) Base crus, &c. ...	3	1	33·3	—	—	—	—	—	—	1	33·3	1	33·3	—	—	—	—	—	—	—	—	—	—	—	—
Totals ...	258	127	49·2	15	5·8	13	5·0	37	14·3	21	8·1	15	5·8	14	5·4	5	1·9	3	1·1	2	0·7	2	0·7	4	1·5

growths, 127, or 49·2 per cent., were Gliomata. Grouping the regions as before, we find there are 91 Gliomata, or 58·7 per cent. of all growths in the Fore-brain. Again, in the Mid-brain this class of tumour predominates to the extent of 50 per cent., but the numbers are few. In the Cerebellum and Pons, including the Extra-cerebellar growths, there are 30 Gliomata out of a total of 78, or 38·4 per cent.

Fibroglioma and fibroma.—These are peculiar to the Cerebellum and Pons and the one Medulla case. The Fibroglioma is a growth which presents the features of Glioma and Fibroma, and I cannot yet say whether it is a distinct pathological entity or a true Glioma in which the conditions of growth are in some way modified by its surroundings. I am inclined to think the latter, and if so it should be included among the Gliomata.

In the peripheral parts of some of the Gliomata in the Fore-brain a tendency to the formation of fibrous stroma with elongation of nuclei is frequently seen, even to the extent of rough capsulation.

Endothelioma.—Endotheliomata are much less common, and they occur practically only in the anterior fossæ of the skull. The regions involved are therefore the Frontal 21, Central 10, and Temporo-sphenoidal 4. Two only affected the posterior fossæ, one in the lateral recess and the other compressing the vermis. To these must be added two Cholesteatomata, which were Extra-cerebellar. This is a curious and interesting point, and it is difficult to explain why the endothelium of the falx, and only the anterior part of it, should be affected to the exclusion almost of all the rest of the great dura matral sheath. There were 35 Endotheliomas of the three regions named, or 25·3 per cent. of all growths for those regions.

Sarcoma.—This group presents some difficulty in classifying, for, as will appear later, there are stages in the growth of the Glioma which, if universal in the section, may be almost indistinguishable from some of the recognized forms of Sarcoma. In any case the group is not a large one. Twenty-one cases only, or 8·1 per cent. of the whole. Six were undoubted round or spindle-celled Sarcomas, 3 of them secondary growths, 1 to suprarenal, 1 to kidney, and the other, melanotic, to the eye. The remainder were primary, and no part of the brain can be said to be exempt.

Carcinoma.—Primary carcinoma is interesting from its comparative rarity. Of the total (15) 1 only is undoubtedly primary, and, from its peculiar appearance, of the Choroid plexus. Seven may have been primary, that is, no growth was found elsewhere, but in one or two only the brain was allowed to be examined. The remaining 7 were secondary—the primary growth being mammary in 3, ovarian, suprarenal, pancreatic and rectal in the other 4.

Tuberculoma.—Verified cases are surprisingly few. It is often diagnosed, but deaths are few. The age-incidence is so young that no doubt large numbers of these patients go to children's and general hospitals. It is also probable that many recover, and I suspect that many of the long survival-periods may include this class of tumour.

Cyst.—The simple cyst deserves attention. I can find record of only 5 in which the true character was verified. All were thin-walled, apparently structureless bags containing clear fluid. One was found *post-mortem* in the mid-brain lying ventrally to the Sylvian aqueduct. The patient died unrelieved by a cerebellar decompression. The others were in the cerebellum, and three came to operation. Two of them were successfully drained and the patients were known to be alive and well six or seven years after ; in the other, by a mistake in localization the exploration was made on the wrong side and the patient died seven days after. The fifth case presented an uncertain symptom picture, though a Mid-cerebellar growth was suspected; no operation was attempted and the patient died fifteen months after the first symptom in the London Hospital. The Medical Registrar has kindly sent me an abstract of the autopsy, at which was found a very thin-walled cyst, of the size of a golf-ball, lying between the two lobes of the cerebellum and pressing down upon the floor of the fourth ventricle. Here is a case that must fill one with regret; operation might reasonably be expected to have been quite successful. If simple cysts were common, that in itself would almost justify exploration in any cerebellar case indiscriminately, but 5 in 258 is 1·9 per cent., and if this is anywhere near the truth simple cyst is a rare condition. Many gliomas, one may say most of the more chronic forms, develop cysts containing semi-gelatinous fluid, the drainage of which often affords more than temporary mechanical relief, but there is little evidence that the ultimate growth of the tumour is to any extent modified.

Papilloma.—Papilloma of the Choroid plexus is a rare condition; it occurred in 3 cases only. In one the growth was felt in the middle peduncle of the right lobe of the Cerebellum, and as much as possible was removed, but the patient died ten days after. Another patient died of pneumonia, and the third died outside, but Dr. Holmes made an autopsy and found a Choroid plexus tumour undergoing colloid degeneration. These growths present the appearance of simple adenomatous overgrowths of the normal tissue, but clinically they are as dangerous to life as any malignant growth, and their situation is such as to be out of the range of successful operation, even if they could be diagnosed with certainty.

The only case of undoubted primary carcinoma, alluded to above, presented the general features of a Choroid plexus tumour, but the columnar cells of the papilloma are swollen into great round cells undergoing active multiplication. In this case also there were many small islands of secondary growth, mostly cortical, the largest being in the left Rolandic region. This region was explored and a cyst punctured, with the escape of 1 c.c. of colloidal fluid. The patient died of respiratory failure on the table. A papilloma, then, may take on highly malignant features.

Cholesteatoma.—One undoubtedly presented the characteristics of this class of tumour. It was Extra-cerebellar in situation, found on operation in the right lateral recess, and removed successfully, but unfortunately the patient died seventy-five days after of sepsis. The tumour was encapsuled, and on incision exuded white, glistening, pultaceous matter consisting largely of cholesterin, and also some large epithelial cells. It proved impossible to preserve the crystals and the section now shows a structureless network with some granular detritus in its meshes. The other was also Extra-cerebellar deeply in the right lateral recess. It was removed successfully piecemeal. The patient was seen a year after, but was in a very poor condition, with all the old symptoms, severe vertigo, and ataxia, with mental enfeeblement and a large hernia. The tumour was described as white, hard, and encapsuled, but no cholesterin was noted at the time of operation. The section now is strikingly like the last.

It is probable that these growths are highly degenerate endotheliomata, and it is perhaps an unnecessary refinement of classification to place them in a group apart.

Pituitary.—The clinical features of pituitary tumour referable to pressure on the Chiasma are so marked that the number 14, or 3 per cent. of the whole, probably represents the true percentage, though only 4 have been verified, all by operation. In 3 of these the tumour was removed more or less completely, and in the fourth partially only, the state of the patient becoming so bad that operation had to be suspended and the patient died nine hours after without recovering consciousness. Of the 3 that survived 2 died in about six months and the third survived three and a half years. It is probable that recurrence took place, and therefore a considerable degree of malignancy must be ascribed to these growths, at any rate if disturbed by operation. This result should be compared with the long survival of pituitary tumours considered below.

Pineal.—Clinically these tumours are undiagnosable as such, the symptoms being referable to Mid-brain and internal hydrocephalus. There have been 4 cases in the ten years, 3 of which have been reported by Howell. The growth, which is of the nature of adenoma or adeno-sarcoma, tends to fill the third ventricle and to extend down the aqueduct of Sylvius to the fourth ventricle, infiltrating more or less widely the surrounding structure.

THE SURVIVAL-PERIOD OF TUMOURS FROM THE APPEARANCE OF THE FIRST SYMPTOM TO DEATH.

I now come to a most interesting part of the subject, an inquiry into the life-history of such tumours as have been verified *post-mortem*, untouched by surgery, which therefore may be assumed to have run a natural course, for it is idle to suppose that, in the present state of knowledge, any therapeutic agent can modify, to any extent, the growth of any of the tumours now under consideration except the tuberculomata. And yet it must be within the experience of every physician that in many cases an extraordinary change for the better occurs during the period of rest and observation in the wards, so that important symptoms, pain, vomiting and the like, disappear, and even optic changes regress. This adds another difficulty in deciding upon the advisability of operative interference.

Table V includes patients who died in the wards and on whom a *post-mortem* examination was made. There were 65 of these, and the average in months of survival from the first symptoms is given for the regions and growths.

In the last column, "Not verified," is given the same average for patients in whom the diagnosis was reasonably certain, but who died outside, or on whom autopsy was not allowed; they number 43.

These periods are of sufficient significance to justify some consideration in detail, especially as the survival-period after operation is of paramount interest, which must be enhanced by comparison with these. The results of operations in this respect will form part of a report to the International Congress of Medicine in 1913.

Glioma.—If we take the 22 gliomata of the Fore-brain as a whole, we find that the patients survived for all sorts of periods from six weeks to nine years, and if we strike a rigid average for all these periods it is found to amount to 16·2 months. But among these 22 is one most exceptional survival-period, nine years, so much so that it seems justifiable to exclude it, and strike an average of the remaining 21. The result of this is to bring the average survival-period down to 10·1 months, and I think this is probably not far from the truth. It may be in excess somewhat because there were three other rather exceptional periods, namely, of four, four and a half, and three years, but on the other hand more cases to deal with might show still more of these long periods.

It will be noticed that the survival-period in cases of tumour of the Frontal region is the longest; the Temporo-sphenoidal region comes next with fewer figures, and the Corona radiata last with still fewer. The Central and Occipital are too few to be considered separately.

The Mid-brain, Ponto-cerebellar and Base (interpeduncular space) may be fairly taken together, though the number of cases is small, 11 in all. The shortest survival-period was twenty-four days, a case of glioma of the Pons, and the longest was two years, also of the Pons. The average survival-period for the 11 cases was 9·4 months, not much less than that for the Fore-brain.

Fibroglioma and fibroma came to operation in all cases but the two on this table.

Endothelioma.—There are too few to base conclusions of any value, 4 in the Fore-brain and 2 in the Cerebellum. These 6 give an average survival of 20·2 months. A rough estimate of the period of growth may be arrived at by averaging the period from the first symptom to the time of operation, in the operation cases, disregarding the result, whether good or evil. Perhaps this may give truer results than at first appears likely, for in some of the cases a fatal issue in any case could not have been long deferred. Thirty-one cases are available for this purpose with very variable survival-periods, for instance, 1 of twenty years or more, another of eighteen years, 3 of ten years, and the rest of all periods from seven years to six months, 1 only of two months. A strict average for all these gives four years as the average survival-period for this class of tumour, and on the whole this may not be far from the truth, though probably it errs on the side of under-estimation.

Sarcoma.—The figures again are few, only 5. The survival-period averages 11·2 months. One patient, however, with a sarcoma of the Optic thalamus, survived four years, which must be an extreme time for

TABLE V.—AVERAGE SURVIVAL PERIOD IN MONTHS FROM FIRST SYMPTOM TO FATAL TERMINATION. NATURE OF GROWTH VERIFIED POST-MORTEM.

Region	GLIOMA		FIBROGLIOMA		FIBROMA		ENDOTHELIOMA		SARCOMA		CARCINOMA		TUBERCULOMA		CYST		PAPILLOMA		NOT VERIFIED		Totals
	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	
(1) Frontal... ...	9	16	—	—	—	—	2	10 : 72	—	—	2	8	—	—	—	—	—	—	6	39	19
(2) Central... ...	2	7 : 108	—	—	—	—	1	4	1	2·5	1	7	—	—	—	—	—	—	3	6	8
(3) Temporo-sphenoidal	6	9	—	—	—	—	1	9	—	—	1	8	—	—	—	—	—	—	2	—	10
(4) Occipital ...	1	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	19	2
(5) Corona radiata ...	4	7	—	—	—	—	—	—	1	5	1	5	—	—	—	—	—	—	1	5	7
(6) Lateral ventricle	—	—	—	—	—	—	—	—	1	1·7	—	—	—	—	—	—	—	—	—	—	1
(7) Pituitary ...	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	48	1
(8) Optic thalamus ...	—	—	—	—	—	—	—	—	2	6 : 48	—	—	—	—	—	—	—	—	1	30	3
(9) Mesencephalon ...	1	5	—	—	—	—	—	—	1	1·5	—	—	2	1·1 : 6	—	—	—	—	2	10 : 18	6
(10) Choroid plexus ...	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	7 : 24	—	—	2
(11) Cerebellum ...	2	12	—	—	1	7	1	3	—	—	1	10	2	13 : 108	1	15	—	—	7	20	15
(12) Extra-cerebellar...	2	6 : 18	—	—	—	—	1	12	—	—	—	—	—	—	—	—	—	—	2	12 : 33	5
(13) Pons	5	9	1	10	—	—	—	—	—	—	—	—	3	7	—	—	—	—	11	21	20
(14) Base	1	·2	—	—	—	—	—	—	1	12	1	24	—	—	—	—	—	—	1	22	4
(15) Not localized ...	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5	48	5
Totals ...	33	—	1	—	1	—	6	—	7	—	7	—	7	—	1	—	2	—	43	—	108

Where the number is more than two, averages are given. If only two, the survival-period for each is given, unless the two periods are almost equal. Decimal points omitted, except in single cases.

sarcoma. If we drop this, the remaining sarcomas give a period of 5·1 months, which perhaps is an under-statement.

Carcinoma.—Seven cases give an average survival-period of 10·1 months, probably an over-statement.

Tuberculoma.—In any case verified Tuberculomata are few, 14, 7 of which came to operation. The 7 that remain give a strict average survival-period of 21·5 months, but in one case the growth had been in existence nine years; without this the survival falls to seven months. However, taking the survival-period to the time of operation, as was done in dealing with the endotheliomata, we find an average survival-period of 17·4 months. The probable explanation of these varied results is that tuberculomas present in their development periods of activity and of quiescence, determined by varying degrees of constitutitional resistance, and it is not too much to assume that such periods of latency may ultimately become permanent. This must surely be the explanation of some of the results shown in Table VI. The importance of an early tuberculin test need scarcely be urged, in view of medical treatment, for the results of surgical interference are far from encouraging.

Simple cyst.—One might expect a simple cyst to be associated with a long survival-period. Only one is forthcoming as fatal without interference, and that had given symptoms for fifteen months (*vide supra*). Mechanical pressure on the floor of the fourth ventricle no doubt was the immediate cause of death. But one can form no conception of how long this cyst had been in existence before making itself felt, and this, of course, applies to all growths. Four came to operation, and in them the survival-period averaged 12·3 months. Apparently these cysts, though rare, are progressive in their enlargement, and their progress is fairly rapid.

Papilloma.—Two cases ran a natural course and, as shown in Table V, survived seven months and two years respectively. Two came to operation and had shown symptoms six months and twelve months to the time of operation. One of these patients was alive four and a half years after. No conclusion can be arrived at in so few instances.

The column "Not verified" includes 43 cases in which the localization was sufficiently clear to justify placing them in the regions named. For various reasons operation was not thought advisable, or in a fair number of cases was refused by the patient. All these patients left hospital alive, and having been written to, the information has come to hand that they have since died, and generally a date has been given. Some died in hospital, but an autopsy was refused. Of course, we have no idea of what class these tumours were, but nevertheless the survival-period is worthy of note. Averaging the 43 cases, we arrive at a survival-period of 24·3 months, a little over two years. The largest number of these, 20, are of Cerebellum and Pons.

TABLE VI.—AVERAGE SURVIVAL-PERIOD IN YEARS FROM FIRST SYMPTOM FOR PATIENTS ALIVE OR FROM WHOM NO INFORMATION HAS BEEN RECEIVED. NATURE OF GROWTH NOT KNOWN.

Region	ALIVE TO DATE		NO REPLY		Total
	Number	Average in years	Number	Average in years	
Frontal	2	2 : 6	5	1·3	7
Central	—	—	3	2·6	3
Temporo-sphenoidal	2	4·6 : 6	5	2·4	7
Occipital	2	13	3	5·2	5
Corona radiata	—	—	—	—	—
Lateral ventricle	—	—	—	—	—
Pituitary	7	9·7	2	2·5 : 0·5	9
Optic thalamus	1	9	1	3	2
Mesencephalon	6	6·5	7	3·4	13
Choroid plexus	—	—	—	—	—
Cerebellum	13	5·7	13	1·4	26
Extra-cerebellar	—	—	3	2·5	3
Pons	5	6·9	12	1·5	17
Base	—	—	—	—	—
Not localized	13	5·2	19	2·3	32
Totals	51		73		124

There remains for consideration Table VI, which seems to me to be of some interest in spite of many weak points. It concerns a total of 124 cases of more or less clinically certain tumours of the Brain, 22 in the Fore-brain, 9 Pituitary, 20 in the Mid-brain, 46 in the Cerebellum and Pons, and 32 not localized at all. These cases fall in an

"Alive to date" column, 51, and of these I have certain information as to their survival and some idea as to their present condition, and a "No reply" column, 73; letters to the patients have been returned through the post.

A glance at the first column suffices to show a remarkably long survival-period. The average, excluding the Pituitary group which deserves special notice, is 6·3 years. Grouping the regions as in former calculations, we find the Fore-brain gives the long survival-period to date of 9·5 years, but this is exaggerated by 2 Occipital cases of eighteen years, 1 probably a tuberculoma.

The Mid-brain and Optic thalamus together, 7 cases, give an average of 6·9 years, and the Cerebellum and Pons, 18 cases, in the same way give a survival-period of six years to date.

The Pituitary groups seem to possess special significance examined in this manner, because the symptomatology of these tumours is so distinctive. It includes 7 cases. All had more or less intense optic atrophy, with progressive loss of sight, and at some time characteristic hemianopsia, though one patient replies that his sight has improved. The average survival-period for all of these is 7·5 years to present date. All of them had been diagnosed as pituitary cases, 2 seem doubtful, but their removal does not appreciably affect the average. Even if this is a gross over-statement it would appear that the growth of these tumours is naturally a slow one, and this is significant in view of the tendency to recurrence after operative treatment (*vide supra*).

In the "No reply" column the survival-period is naturally less striking, because it has to be calculated to the date at which the patient left hospital. It is therefore of little value, but the average survival to that date is 28·4 months. Many of these, of course, may not be alive.

Now I give these figures for what they are worth and they must be received with great caution; but they are sufficiently large to arrest attention and provoke speculation, too large, I think, to be ignored. Probably a certain number are gummata without a history of syphilis, many no doubt are tuberculomata, but it is quite possible that among them are quiescent or latent gliomata or endotheliomata. This is pure speculation, but I would recall the not infrequent instances of a long survival-period among the verified cases, proving that glioma even, and endothelioma certainly, may run very long courses. It is also significant that the cerebellum should supply a proportionately large number of the cases, namely, 26, 13 of which are alive still with an average survival of five and a half years; an equal number from whom no reply has come give an average of 1·4 years to the time of leaving hospital, which perhaps might safely be doubled or even trebled, but equally, of course, some may not be alive. The symptomatology of cerebellar tumours is sufficiently distinctive so that the margin of error in diagnosis can scarcely be very great. The obvious objections to a table of this kind are the initial possibility of error in diagnosis, and ignorance of the nature of the lesion; so much has to be taken on trust, and the danger is that it may be taken too literally.

An Inquiry into the Life-history of the Glioma from the Histological Standpoint.

Of all the growths that affect the brain the glioma stands first both in frequency and importance.

As shown above, of 258 cases in which the nature of the growth was verified 127, or 49·2 per cent., were of this class. Most of these I have examined myself, thanks to the labours of our pathologists during the last ten years, and they present a bewildering variety of histological appearances, and the difficulty of placing some of them seems almost insurmountable. This difficulty is rendered all the greater from the fact that the same tumour may present, sometimes within the compass of an ordinary section, grades of change of great variety, so that at one end of the section we are looking at an apparently innocent growth, and at the other a richly cellular mass, more like a malignant sarcoma, or in another place an area of necrosis. On the whole, this variety of appearances seems to be distinctive of the gliomata, and occurs more often, and in a higher degree, among them than in any other of the intracranial growths. To arrive at a just estimate of the malignancy of a glioma it is really necessary to make sections from the periphery to the centre, and this of course, is not always possible.

The original conception of a glioma is that of a simple overgrowth of the connective tissue element of the brain. It is not common to find a tumour which presents this simple character throughout; the nearest approach to a typical instance is:—

Case 1.—This is from T. H., a man aged 42 (Sir W. Gowers), who had presented symptoms referable to the left Frontal region of eighteen months' duration. Unfortunately the operation notes have been mislaid, and one can only find that the left Frontal region was explored (Sir V. Horsley), and some part of the tumour removed, from which this section was made. The patient died at home not very long after, but the reply is very indefinite. (Fig. 1.)

The noteworthy histological features (fig. 1) are[1]:—

(1) A fine, loose-meshed glia reticulum.

(2) Delicately stained, barely visible glia-cells, with three or more branching processes, which divide into a fine reticulum which forms the stroma or connective tissue basis of the tumour. To show these elements a counter-stain, such as Van Gieson's, is necessary.

(3) Scattered over the section in not excessive numbers are the glia-nuclei, always deeply stained by hæmatoxylin. I call these "glia-nuclei" to distinguish them from the more histologically definite "glia-cells." Possibly they also are cells with an invisible cytoplasm. The term is provisional only. They should be fairly uniform as to size and not grouped, but even in this apparently innocent quiescent picture these cells tend to show an arrangement in circles or segments of circles, a feature to be referred to later when considering the more malignant types.

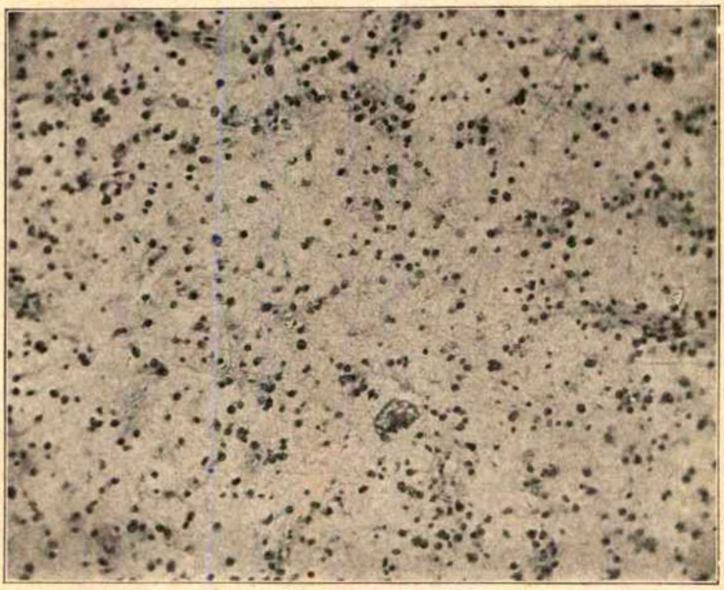

FIG. 1.—Case 1. Section of a glioma of a low degree of malignancy. Frequent arrangement of nuclei in circles or semicircles of very varying diameters, also in places in almost straight lines.

(4) The blood-vessels are few and their walls lined internally by a single layer of flattened endothelial cells.

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[1] In preparing the photomicrographs throughout a Zeiss D. objective has been used without correction. This has the advantage of giving sufficient magnification, without requiring great illumination, but at the expense of complete flatness of field.

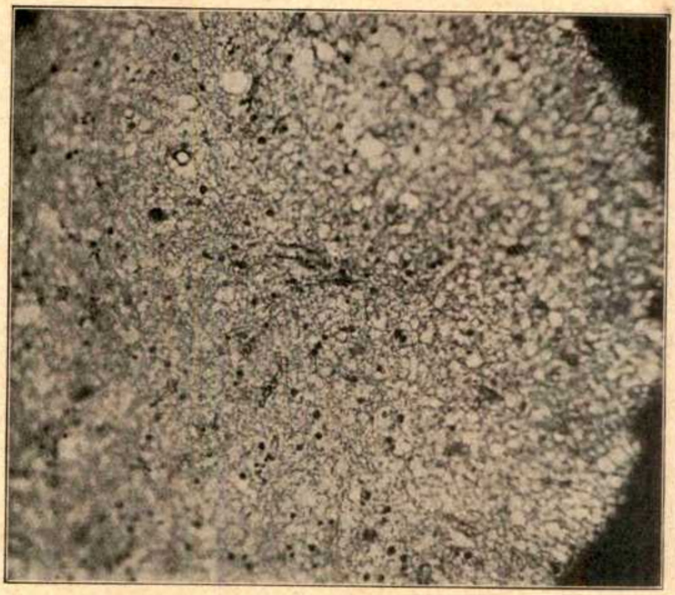

FIG. 2.—Case 2. Quiescent glioma. Very few glia-nuclei. Some cyst formation. (Section not flat.)

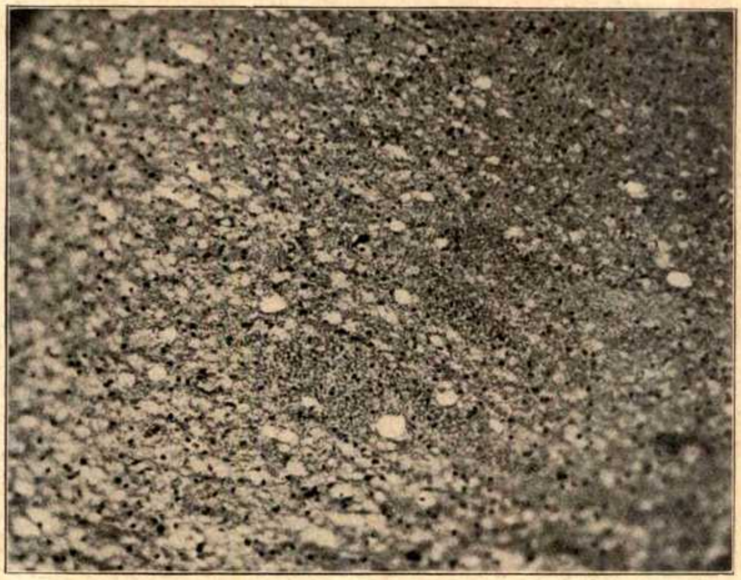

FIG. 3.—Case 2. From another part of the same tumour as fig. 2. Hæmorrhages in the centre of the field.

These are the characteristic features of the simple (?) non-malignant phase of a glioma.

There is reason to suppose that a glioma may retain these apparently innocent characters for an indefinite period; in fact, the clinical history of many cases can be explained in no other way. It is conceivable that in such a phase the growth may be no more malignant than a lipoma. Moreover, rarely, it may be removed successfully without recurrence.

In confirmation of this statement is the following case:—

Case 2.—A girl, E. B., aged 19 (Dr. Bastian), admitted in 1904 with marked clinical evidence of cerebellar tumour. First symptom one and a half years before. Operation (Sir V. Horsley) disclosed a tumour the size of a hen's egg, occupying the left lobe, vermis, and part of the right lobe, which was removed. The patient is still alive, eight years after, and in excellent health. There is no bulging of the wound, so probably no tendency to recurrence. But owing, no doubt, to considerable permanent destruction of cerebellar tissue, she still presents many of the symptoms—ataxia and paresis of the legs—of a cerebellar lesion. She is so well that she is about to join her father in Canada. (Figs. 2 and 3.)

Sections of the tumour removed (figs. 2 and 3) show a rather thickly felted stroma, so much so as to hide the glia-cells; small cavities are seen all over the section, indicating cyst formation so common in all gliomas. The glia-nuclei are relatively few, another suggestion of quiescence. Hæmorrhages may be seen, but possibly these may be due to operative manipulation.

Unfortunately this is a rare result, much too often the sequel is recurrence.

Now, assuming that there is such a thing as an innocent, latent, quiescent glioma, in what elements of the growth do the changes occur which constitute malignity, and what are those changes? The physiological process in action would appear to be that of active proliferation; this has its seat in: (1) The normal glia-nuclei of the stroma; (2) the glia-cells; (3) the blood-vessels.

(1) *The nuclei.*—The number of these may be variable within limits which may justify our considering the appearance as of an innocent type. But one evidence that these nuclei may be sharing in the awakening of proliferative activity is their arrangement into circles or even lines, as has already been hinted in fig. 1. To what extent they share in the ultimate richly nucleated and cellular growth of the malignant glioma I am unable to say.

(3) *The glia-cells.*—The evidence that the glia-cells play a most, if

not the most, important part in malignant activity seems to be quite clear. The alteration from the normal consists in: (*a*) Enlargement of the glia-cells; (*b*) increase in their number, though still retaining their morphological character, dendritic processes for instance; (*c*) multiplication of their nuclei; dislocation of these to the periphery of the swollen cell; (*d*) disappearance of the original cell, and independent existence of nuclei, which now resemble round sarcoma cells in a state of active multiplication.

This, I think, must be the sequence of events in many, if not all, of the malignant types. But it is possible that new cells, having some resemblance to altered glia-cells, may have a different origin, and the resulting growth may then more nearly resemble a true large-celled sarcoma. This is a difficult point, and it may be that the glia-nuclei may bear a larger share in this process than has been suggested above. It must not be forgotten that all these changes, in varying degree, may be seen going on in the same growth.

In illustration of the foregoing remarks are the following cases:—

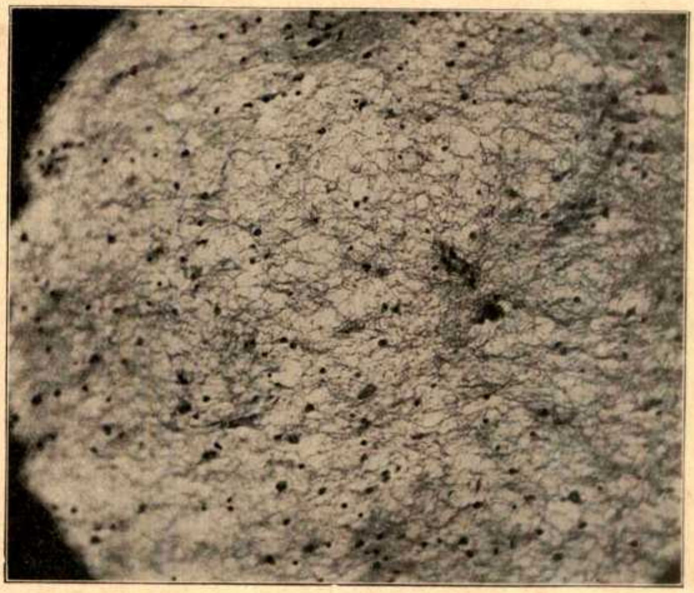

FIG. 4.—Case 3. Glioma of innocent appearance. Glia-nuclei small and few. Glia-cells difficult to see; one large one to right of centre.

Case 3.—A man, W. E. T., aged 50 (Dr. Buzzard); symptoms of ten months' duration. A fit followed by right hemiplegia and partial aphasia.

Operation (Sir V. Horsley), left Central, discovered a large subcortical tumour, a cyst the size of a hen's egg, was drained, and part of the wall excised, from which the section was taken. A considerable hernia resulted, and later sepsis showed itself. Five weeks after, another operation was performed, but the notes are here defective. A febrile condition set in; he became quite aphasic, and died three months after admission. (Figs. 3, 4, 5, 6.)

Fig. 4 shows a simple, sparsely nucleated, somewhat cystic reticular stroma with only one doubtful glia-cell in the field. No evidence of active growth.

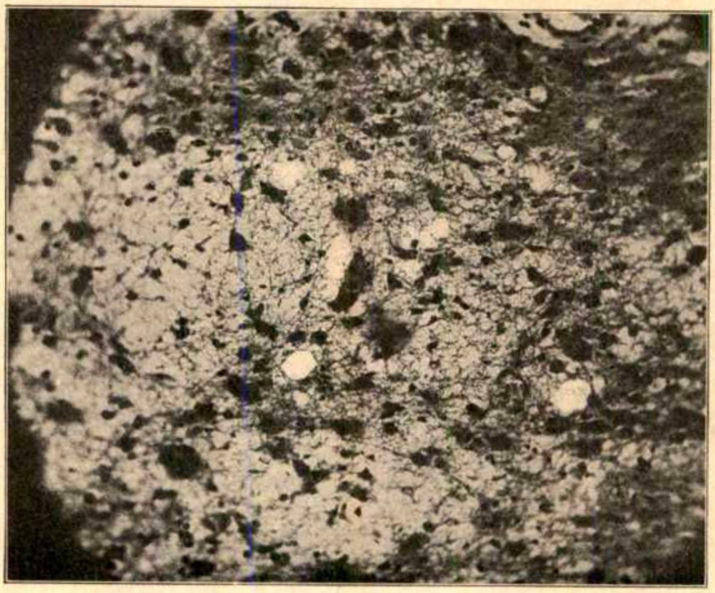

FIG. 5.—Case 3. Evidence of activity. Glia-cells enlarging, their nuclei multiplying, shown in two cells in centre of field.

Fig. 5, the same stroma, but a considerable, not excessive, number of large glia-cells variable in size, some containing more than one nucleus. Glia-nuclei more abundant. General appearance of activity.

Fig. 6 from another part of the section; the stroma is more condensed, and glia-nuclei are in greater abundance than in the last two fields. The glia-cells are also here in some number, and of very variable size. Their proliferated nuclei are situated in rings round the periphery of the smaller cells; in places these rings are all that remain.

Case 4.—T. W. A., a man, aged 47 (Dr. Taylor); symptoms dated only fifteen weeks before admission; paræsthesia of the left arm and leg in attacks

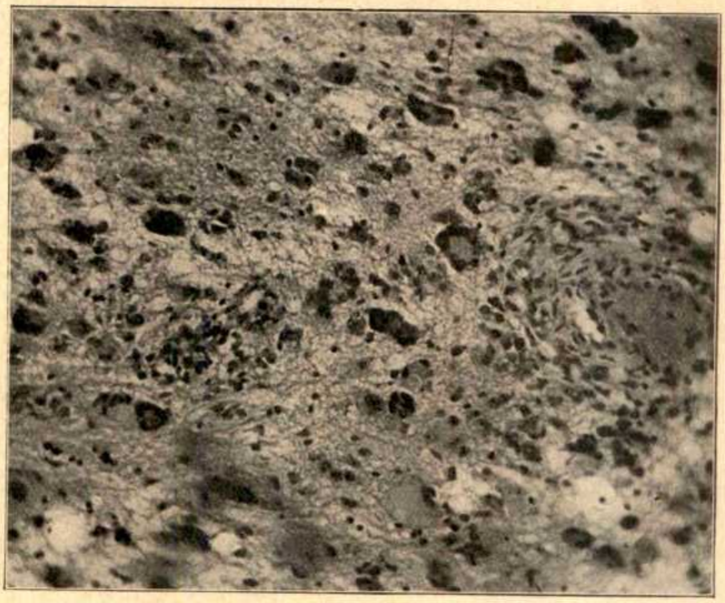

FIG. 6.—Case 3. From a more active part of the same glioma as figs. 4 and 5. Proliferation of nuclei of glia-cells, disappearance of cells, leaving rings of nuclei.

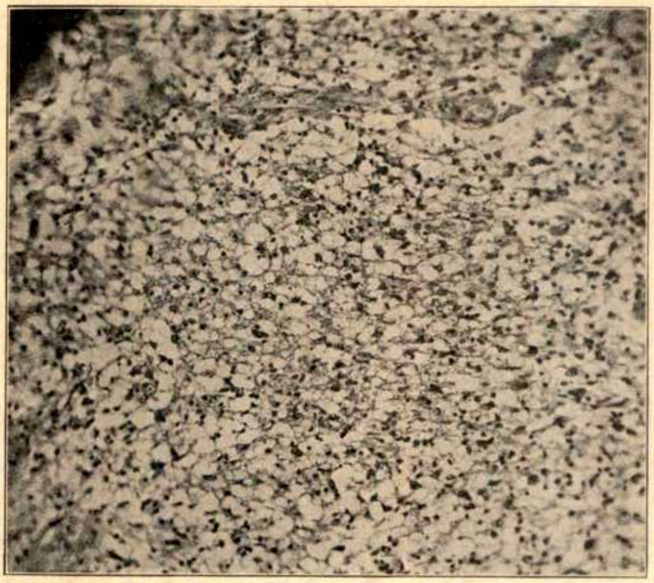

FIG. 7.—Case 4. Glioma. Stroma finely reticular and cystic. Nuclei small, but in considerable numbers. Glia-cells of normal appearance and number.

of three months' duration. Left hemiparesis and anæsthesia on admission. Double optic neuritis and left hemianopsia. Operation (Sir V. Horsley) four days after admission. Right Parieto-temporal not much bulging at first stage, but this was more evident at the second five days after. A large tumour subcortical to the right post-central region was found extending to the descending horn of the lateral ventricle, forward to the lower part of the precentral convolution, and back to the supra-marginal region. It was removed as far as possible. The patient made a fair recovery, but considerable bulging resulted, and there remained a left spastic hemiplegia. I hear from his wife that he died five and a half months after operation outside the hospital. (Figs. 7, 8, 9.)

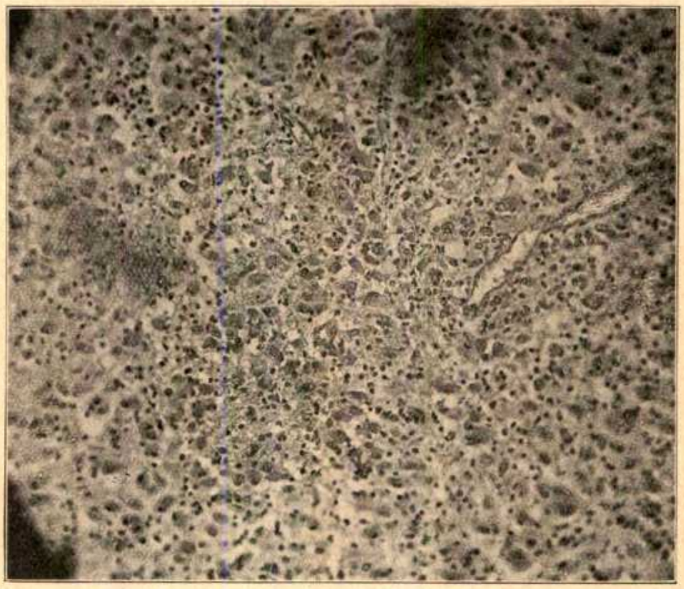

FIG. 8.—From same as fig. 7. Richly cellular, but glia-stroma retained. Cells mostly oval with a nucleus at one pole.

Fig. 7 shows a fine specimen of the simple type of glioma. The glia-nuclei are fairly abundant, but small, and with little evidence of proliferation. The stroma, however, has a cystic appearance, and the glia-cells are few and of normal character.

Fig. 8.—Here is a centre of activity, many definite cells of various size, some possessing glia-cell characteristics, others barely recognizable as such. Some with more than one nucleus, others with only one, but at one pole of the cell. I am doubtful of the true interpretation of this appearance, which is a common one. The cells are almost too small for

swollen glia-cells, they are mostly uni-nuclear. They may be swollen "glia-nuclei" and not glia-cells. Here and there the tendency to ring arrangement of nuclei is also to be seen in places.

Fig. 9.—In another part of the section is an area of necrotic degeneration, and in the neighbourhood of these areas one repeatedly finds thrombosed vessels; this will be referred to later.

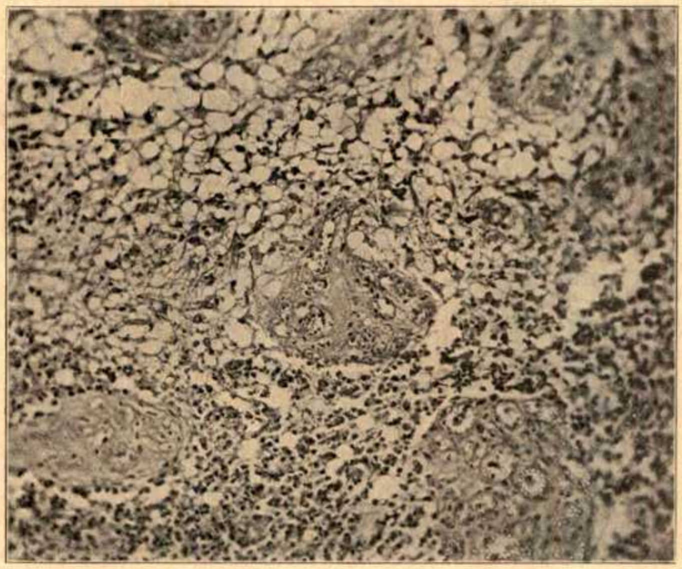

FIG. 9.—Case 4. Vessels thrombosed, on the border of an area of necrosis. Lower half of section.

Case 5.—T. J., a man, aged 38 (Sir W. Gowers), was admitted in March, 1904, with a seven months' history of failing memory, fits, development of the dull, lethargic mental state of a frontal tumour, and intense double optic neuritis. A month after admission the right frontal region was explored (Sir V. Horsley), and a cystic tumour was found presenting as a small patch 1 in. in diameter in the middle of the right middle frontal convolution. On incision this proved to be the wall of a large cystic cavity; this was removed as much as possible, the area of removal reaching to the lateral ventricle. He made a good recovery, and left hospital, with some bulging of the wound, optic neuritis much subsided, and mental state natural, two months after. The hernia, mostly fluid, increased, and it was tapped with some relief three months after operation. The subsequent history of the case will be considered later under the head of "Recurrence." (Figs. 10 and 19.)

Fig. 10.—A section of the tumour removed at the first operation. The glia-stroma presents no greatly abnormal appearance, it is somewhat condensed and cystic, and the glia-nuclei are not excessive in number. But what I take to be the glia-cells are in great numbers, large and swollen, yet with in many instances their dendritic processes retained. In some the nucleus seems to have disappeared, in others it is displaced to one pole of the cell, or in others there is more than one. This seems to me a more convincing illustration of the part played by the glia-cells than any I have yet shown. In some parts these cells have multiplied to the extent of obscuring all the other features of the original glioma.

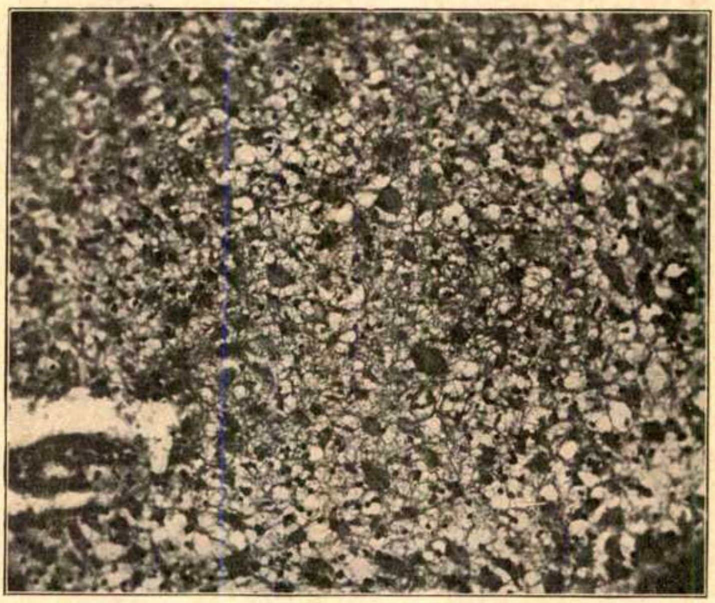

FIG. 10.—Case 5. General glia-cell enlargement and multiplication, suggesting considerable malignant activity. The cells retain their processes, many are still uni-nuclear, or devoid of nuclei. The stroma is denser than in the last case, and cyst spaces are numerous.

The following is yet another instance. In spite of the very malignant appearance of the growth, this patient is still alive.

Case 6.—F. B., a man, aged 35 (Sir W. Gowers), admitted July, 1908, with a six months' history of failing memory, faints, headache, vomiting, diplopia, and failing vision. His mental state, defective memory, "dreamy states," were suggestive of a Temporo-sphenoidal tumour, and two months after admission a large cystic tumour was removed (Mr. Armour) from the left Temporo-sphenoidal lobe. After operation he was quite aphasic for a time, but this improved, so that four months after he could talk well and get about. But he remained emotionally unstable, and a large hernia cerebri developed. He was readmitted three years after operation with an enormous hernia. Mental condition vacant and stupid, memory and attention very poor. Right hemiplegia. Vision: right, blind; left, $\frac{3}{60}$. Optic disks: right, consecutive atrophy with + 4D. of swelling; left the same, but to a less degree. From the reply I have received I judge that he is in much the same condition, perhaps worse, than when last seen. (Figs. 11, 12, 13, 26.)

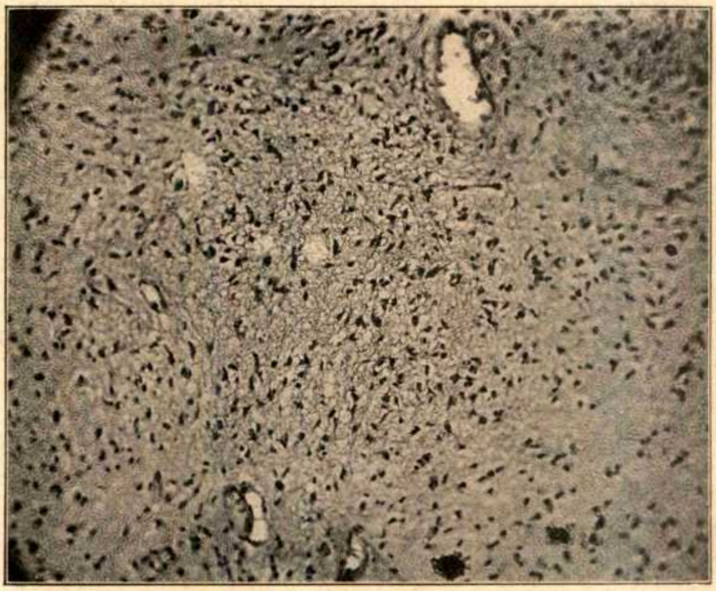

Fig. 11.—Case 6. Glioma. Stroma rather dense. Nuclei present a shrunken angular appearance. No marked evidence of activity.

Fig. 11.—All parts of the growth show some evidences of its gliomatous nature, and this part has almost an innocent appearance, but the glia-nuclei, if such they are, present an unusually angular appearance.

Fig. 12 shows a great multiplication of glia-cells, less convincingly glia-cells perhaps than in the last case, but still retaining in many of them the multipolar form, and more closely packed. Multinucleation is also well shown. But some of the cells are oval and uni-nuclear, as in fig. 8.

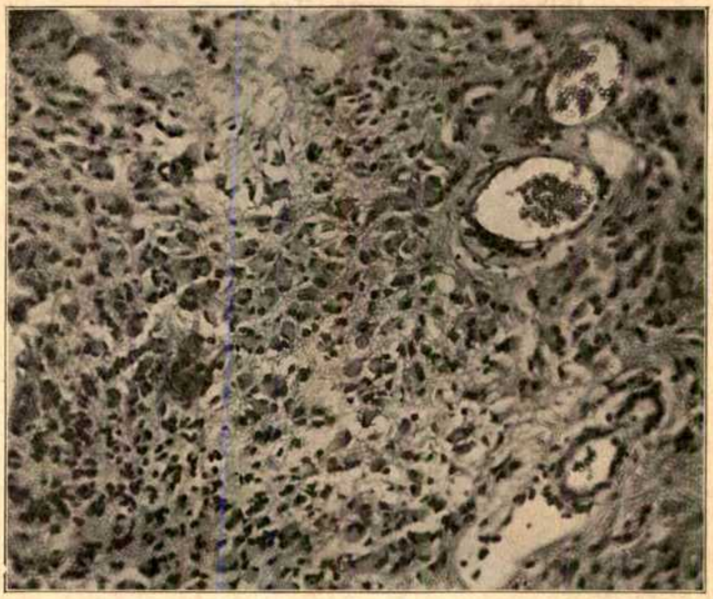

FIG. 12.—Case 6. From an active part of the growth. Many swollen multinucleated glia-cells. Some oval with single nuclei, as in fig. 8.

Fig. 13 shows the same characters considerably enlarged.

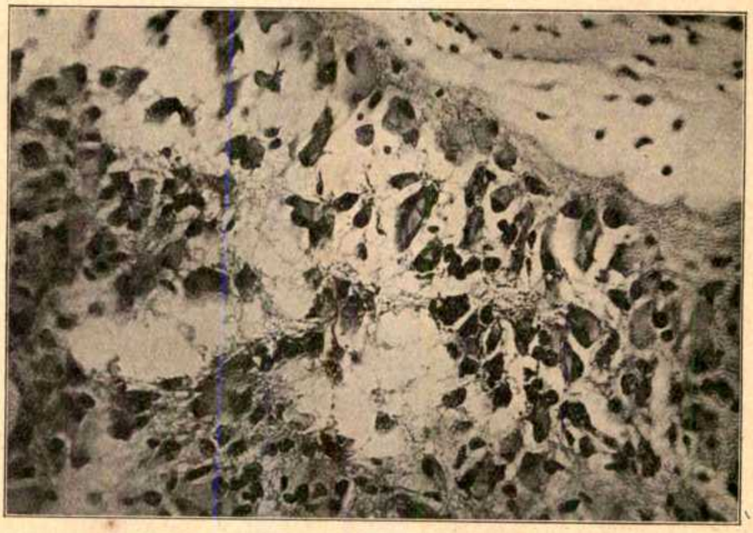

FIG. 13.—Case 6. The same appearances as in fig. 12 enlarged.

Case 7.—H. C., man, aged 31 (Sir W. Gowers). The first symptom, sudden failure of vision and memory, dates only six months before death. He presented the typical mental state of a frontal growth, disorientation in time and space, jocular mania "Witzelsucht," anosmia, double optic neuritis passing to atrophy, with great amblyopia. An operation was arranged for, but he died the day before, eight days after admission. This is one of the most rapid cases. *Post-mortem* a tumour was found involving the median and orbital surface of the left frontal lobe extending into the right. (Fig. 14.)

Fig. 14.—The field is packed with large cells of varying sizes, and containing one to six nuclei, generally peripherally disposed. The cells contain a faintly staining granular cytoplasm and some are angular, but the original glia-stroma is very little in evidence. The annular arrangement of the escaped nuclei is well seen and within their circles may be seen the remains of the parent cell. This picture I regard as the extreme result of glia-cell proliferation. If not viewed by the light of the preceding cases it might well be regarded as a large cell sarcoma.

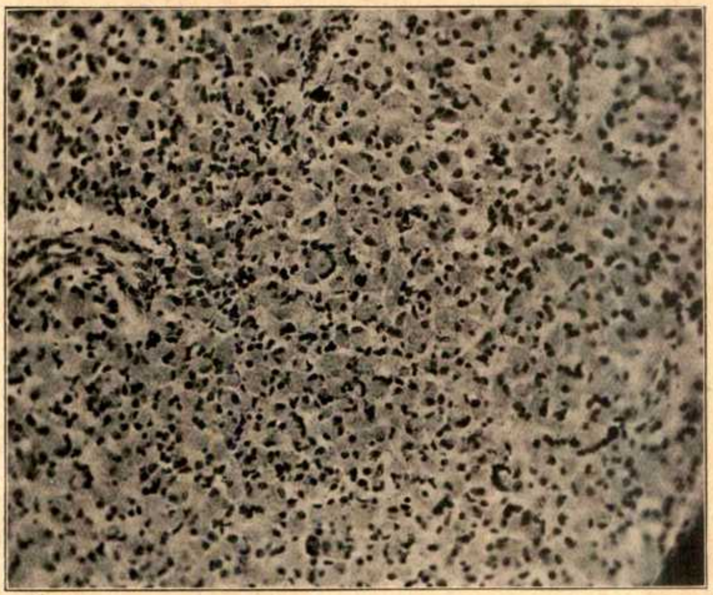

FIG. 14.—Case 7. Closely packed large cells; cytoplasm faintly stained; multinucleated; nuclei peripherally disposed. Disappearance of parent cell, leaving a ring of nuclei.

Gliomas are not commonly multiple, and metastasis is almost non-existent. The following is a case of two tumours, one of which was a glioma and the other probably an angio-sarcoma.

Case 8.—W. E. G., aged 51 (Dr. Taylor). Another very rapid case, five months from first symptoms to death. He gave a history of left hemianopsia and rapidly failing vision to complete blindness. He was in hospital under a month, during which he became more and more stuporose and died. *Post-mortem* a large tumour was found occupying most of the right occipital and temporal lobes, and another small one was in the right marginal gyrus, about 1 in. in diameter, hard and deeply congested. (Figs. 15, 16, 22.)

Fig. 15 from the large occipital tumour is obviously a glioma.] [In spite of the rapid history this section shows little evidence of great activity. Probably sections from other parts of the growth would discover appearances of malignancy similar to those in the preceding cases.

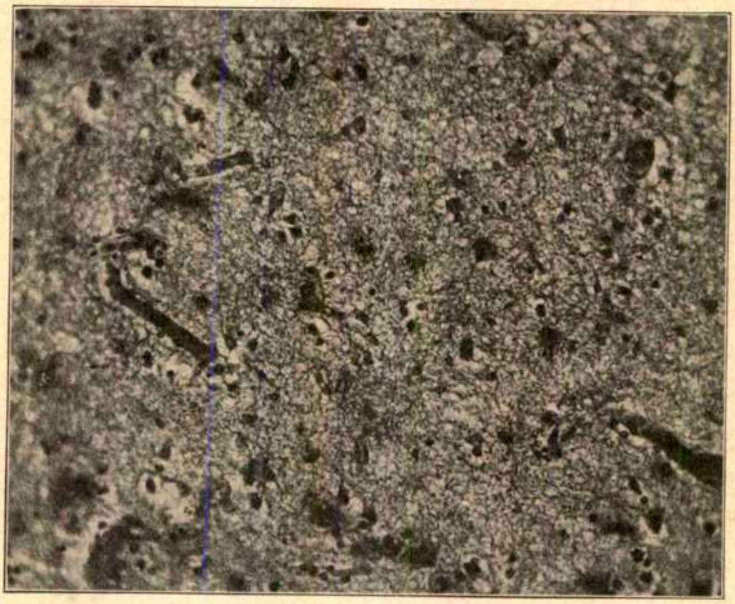

FIG. 15.—Case 8. Occipital glioma. A densely reticulated stroma with large and not very many glia-cells; a few glia-nuclei.

Fig. 16 is a spindle-celled growth with many vessels, an angio-sarcoma.

I do not suggest any pathological connexion between the two growths, but the case is interesting from its comparative rarity.

The next stage in this moving picture of proliferative growth that demands attention is that concerned in the further progress of the nuclei liberated by the disappearance of the parent glioma-cells, by which an appearance is produced different from that hitherto described in this account.

Malignant activity is plain enough in some of the sections figured above, but to my mind it is still more so in the stage to which we have now arrived; in fact, the histological picture is that of forces suddenly brought to a standstill when in full play. In illustration of this—

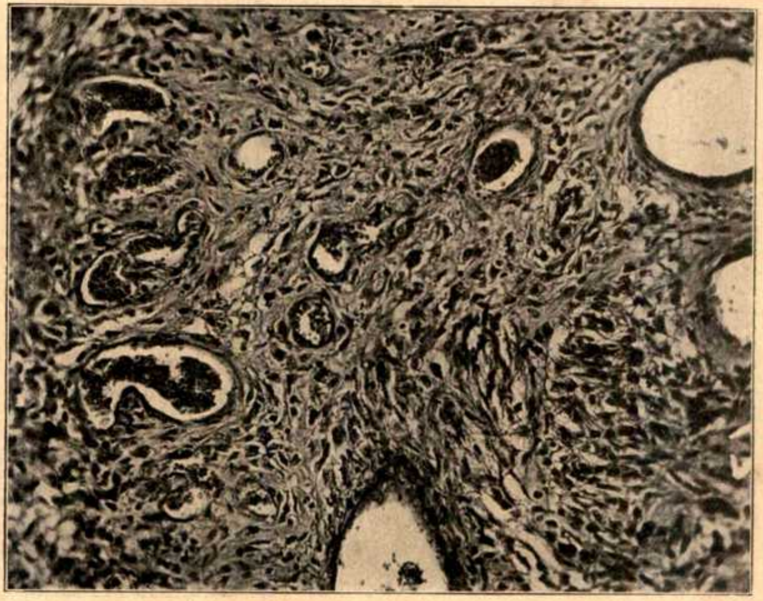

FIG. 16.—Case 8. Second small, hard, vascular tumour in straight marginal gyrus; an angio-sarcoma.

Case 9.—A. M., aged 37 (Dr. Beevor), admitted July 1, 1904, with a long history, two years, of fits, no details given; ten months, visual symptoms suggesting left hemianopsia, which was confirmed on admission; four months, fits beginning in the left foot. No hemiplegia, no optic neuritis. Readmitted in December, 1904, seven months afterwards; two months after this optic neuritis appeared, a post-central growth was diagnosed, and operation followed (Sir V. Horsley), February, 1905. A large cystic tumour, cyst within cyst, was shelled out. The patient made a good recovery and was discharged as "cured." He was readmitted in June, 1906, four months after operation, with progressive left hemiplegia and hemianæsthesia, but the optic disks were clear and showed no evidence of past neuritis. I heard from his widow that he died in September, 1906—i.e., nineteen months after operation. (Figs. 17 and 18.)

Fig. 17.—Section of the growth, which includes a piece of cortex, under which the growth lies. This is a cellular glioma, rich in large swollen cells, but with their processes yet retained, and some of the glia-stroma reticulum between, also rings of nuclei, many of small diameter, showing within their circumference the remains of the parent cell.

Farther away from the cortex the large cells are in still greater abundance, packed closely and also crowded with nuclei round about them.

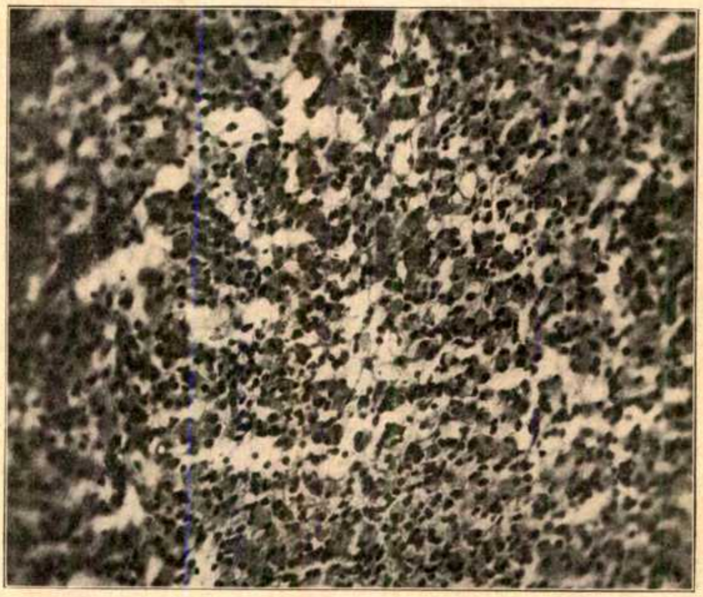

FIG. 17.—Case 9. Richly cellular and nuclear glioma. Of the large cells many are multinuclear, and many are disappearing, leaving a ring of nuclei.

Fig. 18.—Farther still we find the nuclear elements in such numbers as to obscure the parent cells or their remains, though by careful focusing many may be seen. The picture now is that of a small round-celled sarcoma, but by no effort of focusing can one see any cytoplasm surrounding these nuclei. Possibly recent special stains may show that these are the nuclei of new cells, but I have not yet had the opportunity of seeing the result of their use.

The arrangement of these nuclear elements of the growth is also characteristic; in all parts of the field are circles or half-circles, rarely straight lines, presumably in whatever plane the section is made. The circles may be small, no larger than the circumference of the parent cells from which they come, but they show a tendency to an ever widening radius, suggesting lateral division of neighbouring nuclei. The semicircles of course suggest a slight tilting of the plane of that circle, so that half is in one section and the other half in the next above or below. So frequent are the rings in any given plane that one is tempted to conclude that every nucleus all over the field is one of a little circle of its own in another plane. This annulation, as representing independent centres of growth infinite in number, bring home to the mind of the observer the intensity of the exuberant activity that constitutes high malignancy. No doubt this annulation has been seen often enough by other observers, for it can be seen in all these richly cellular growths.

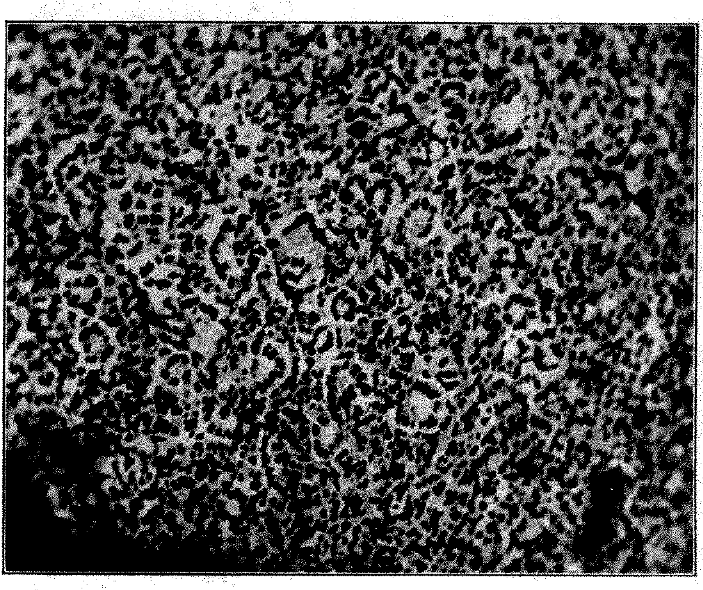

FIG. 18.—Case 9. Illustrating ring formation, or annulation. In a thick section underlying features tend to confuse a photograph; therefore in this figure some of the details immediately adjacent to the most obvious rings or semi-circles have been blocked out.

Annulation has been demonstated as occurring in a greater or less degree in many of the preceding figures. In fig. 1 even it is seen, and in this also can be seen the tendency to formation of straight lines, which may be a common arrangement, but it would naturally be less evident in a crowded picture. A similar grouping of nuclei may be seen in the growing brain (see the article on the "Cyto-architecture of the Cerebral Cortex," by Bolton and Moyes, in this volume of *Brain*, p. 14, fig. 7).

From the foregoing observations one seems to be justified in conceiving an ascending scale of malignity from the slow-growing or quiescent overgrowth of glia-tissue to an anatomical picture resembling grossly malignant sarcoma. These may be, and are, called glia-sarcoma, but I have avoided using the word; it seems unnecessary and perhaps misleading to have another word for what would appear to be a phase of growth only, if that is the right reading of these changes.

Recurrence.—In several cases an opportunity has been afforded of examining the growth removed by operation and subsequently the recurrent growth at a second operation, or *post-mortem*. The two cases following are the simplest, the others present such complicated appearances and would require so many photographs to bring out all their features that I have thought it wiser to omit them.

Case 5.—Sequel (*vide supra*, p. 87). Three months after removal of a large cystic frontal tumour a large resulting hernia was tapped with some relief. The histological appearances of the growth removed at operation are shown in fig. 10. He was readmitted five months after operation and stated that he had been practically well until six weeks before, since when he had had two to four fits a week and he became mentally dull and lethargic. He was in hospital for a month, and left much improved mentally but with a large fluid hernia as before. During stay in hospital he had one general convulsion. He was readmitted for the third time nine months after operation with a progressive left hemiplegia and much mental dulness and apathy. His condition not improving, the flap was reopened nine days after admission and a large quantity of clear fluid was found in a cavity, the site of the original tumour. At the bottom of this cavity a mass of growth was seen and removed. He did not recover consciousness and died the next day, the temperature rising to 104·8° F. (Fig. 19.)

Fig. 19 shows very similar appearances to those of the last case, fig. 18. No glia-cells can be seen at all. Annulation is quite distinct and there is no superficial resemblance to the original growth. It shows every appearance of rapid recurrence and would no doubt eventually have filled the cavity left by the old tumour.

Case 10.—This is a more doubtful illustration of recurrence than the last, because the time which elapsed between the removal of the growth and the *post-mortem* is so short, eleven days only. But the time element in pathological events is always an almost unknown factor.

W. O., a man, aged 42 (Dr. Batten), admitted November 4, 1910, with an eighteen months' history of frontal headache and frequent faints, eight months failing vision and memory, and slight sphincter weakness. He showed some of the mental symptoms of frontal tumour, which became more definite later, and intense optic neuritis and swelling, rather more pronounced on the right side.

Twenty-five days after admission the right frontal region was explored by

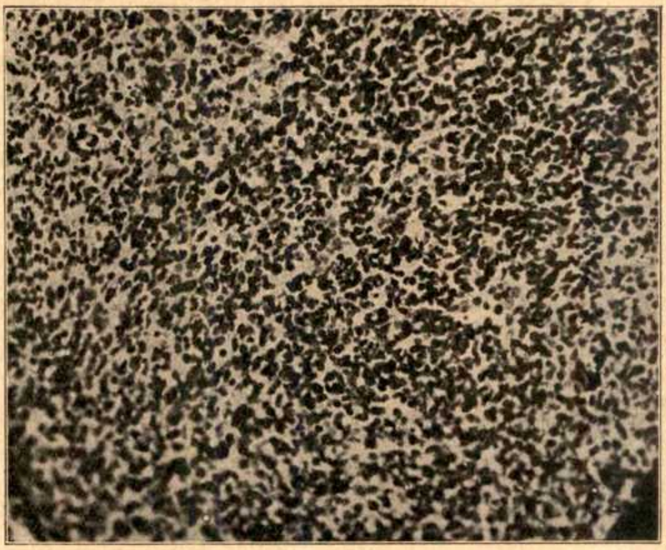

FIG. 19.—Case 5. Section of mass of recurrent growth, resembling closely fig. 18. Annulation is obvious, also a tendency to arrangement in lines more or less straight.

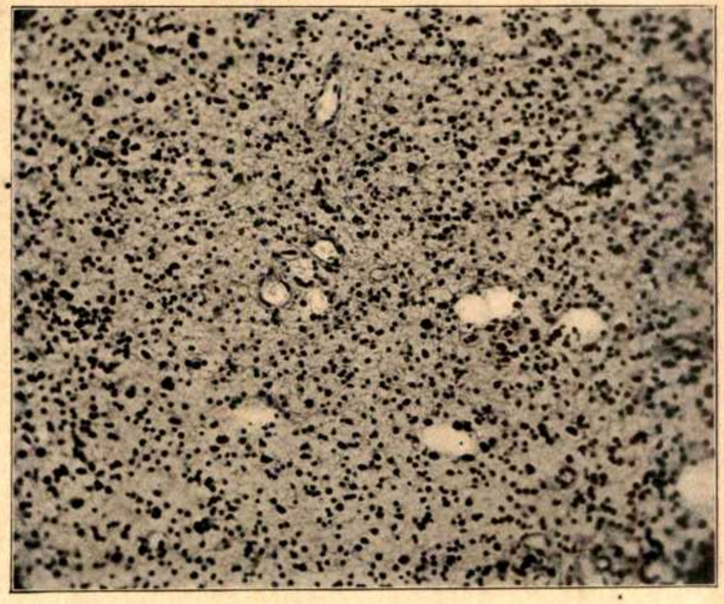

FIG. 20.—Case 10. From the glioma removed at the second operation (the first was exploratory). The stroma is finely and normally reticular, and the glia-cells few and almost invisible. But the nuclei are in great number, and annulation well shown all over the field. Two normal vessels are seen on each side of an annulus, to the left of the centre.

incision (Sir V. Horsley); the substance was thought to be abnormally firm and nothing was done. The patient made a good recovery and the neuritis subsided rapidly. He was discharged to the Convalescent Home, but was readmitted four months after operation, with headache again, mentally emotional and slow cerebration. There was an increasing hernia, and a renewal of the optic disk swelling. Another operation was then performed. On exposing the frontal lobe a large cyst burst, which was partly removed. There was no relief this time, the temperature fluctuated between 100° and 104° F., and patient died eleven days after. At the autopsy the main tumour was found in the mesial side of the right frontal lobe extending over to the same side of the left frontal and forward to within 1 cm. of the frontal pole and back to the anterior horn of the lateral ventricle, involving the genu of the corpus callosum, from which it may have originated. (Figs. 20 and 21.)

Fig. 20.—A section of the tumour removed eleven days before death is a fine example of a glioma in which the glia-cells seem to be little affected. The reticular stroma also is fairly normal and also the vessels. But the field is richly nucleated and annulation is evident. The nuclei are variable in size and in places still more numerous than in this figure. This is a good example in illustration of a probable share taken in proliferation by the simple glia-nuclei.

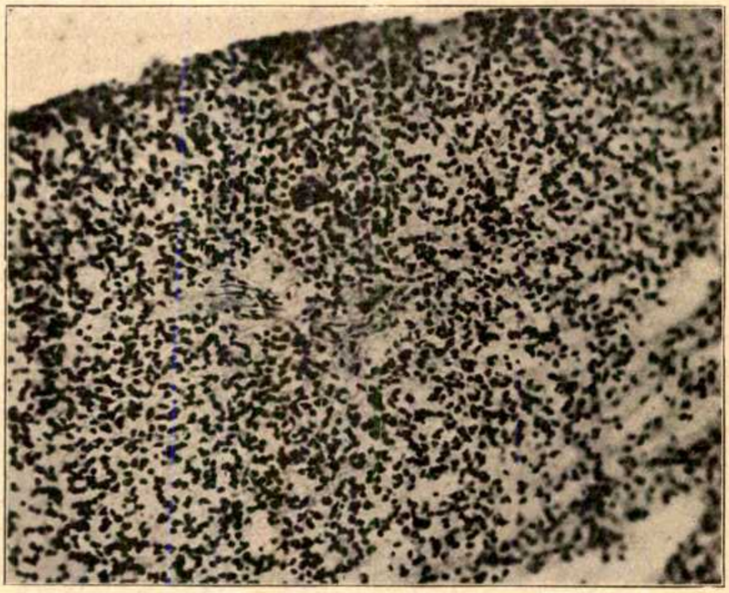

FIG. 21.—Case 10. Recurrence. From the growth removed (*post-mortem*) eleven days after the second operation. The appearances are almost exactly similar to those of fig. 19.

Fig. 21.—A section of the growth removed *post-mortem.* Unfortunately most of the section is of altered brain substance, but there is one portion of it sharply delimited, and evidently growth which resembles in every respect the recurrent growth of the last case; little if any glia-stroma is to be seen, but somewhat irregular annulation is visible all over the field.

If these appearances are to be accepted, and I offer them with the greatest possible diffidence, one is forced to infer, on pathological grounds alone, that surgical interference, exploration, or manipulation, with few notable exceptions, is liable to awake into greater activity a tendency to exuberance which perhaps may be almost latent at the time.

The Rôle of the Blood-vessels.

What part do the blood-vessels play in the growth and progress of the glioma?

In vascularity these growths show wide variations, from one or two small thin-walled vessels to the field, of which the endothelial lining is marked by a few nuclei at regular intervals, to the development of numbers resembling an angioma.

The larger vessels should present the natural appearance of an arteriole, but sometimes one finds, especially in the more angiomatous forms, a thickening and condensation of the glia-tissue round about the large vessels as in fig. 22, belonging to Case 8, in which the second tumour was an angio-sarcoma.

But in many cases the small vessels show great swelling and proliferation of the endothelial intima. Fig. 23 is from another case of recurrence after removal. The recurrent growth was more vascular than in the cases above mentioned, and the stroma presents a fibro-sarcomatous appearance, which was absent in the original growth. This section illustrates the swelling and proliferation of the endothelial intima. The vessel may remain pervious, but if the process continues the ultimate result is complete blocking of the lumen and a picture that is almost unrecognizable as a vessel at all may result.

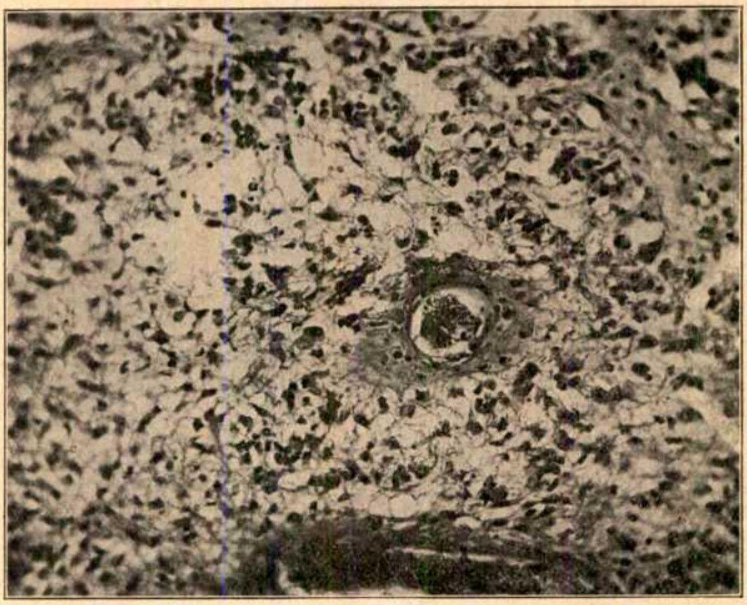

FIG. 22.—Case 8. Detail from the smaller tumour, of which fig. 16 gives the general characteristics of angio-sarcoma. A vessel surrounded by condensed, almost fibrous tissue. In this particular situation the stroma somewhat resembles that of coarse glioma, but it is exceptional, and probably a necrotic effect.

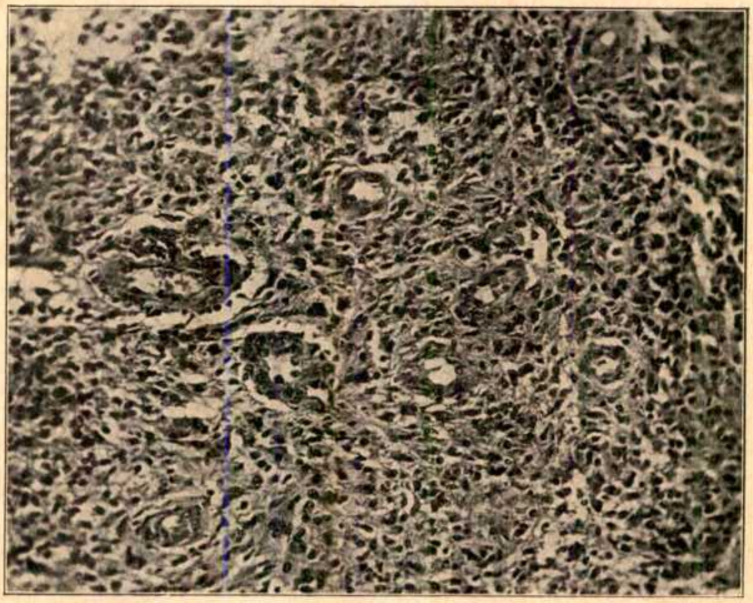

FIG. 23.—From a recurrent growth after removal of the original tumour from the post-central area. The small vessels show swelling and proliferation of the intimal endothelium, but many are still pervious.

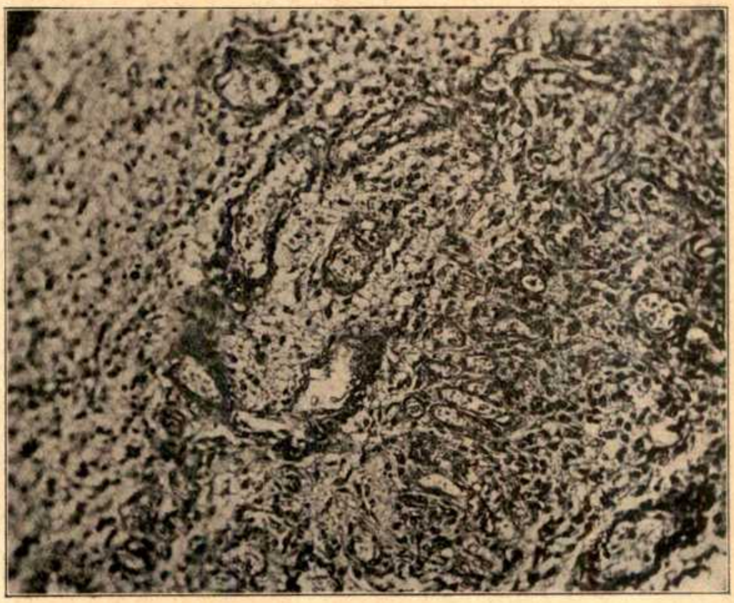

FIG. 24.—Case 11. From a large glioma of the centrum ovale. Great vascularity, but intimal proliferation is not shown in this section.

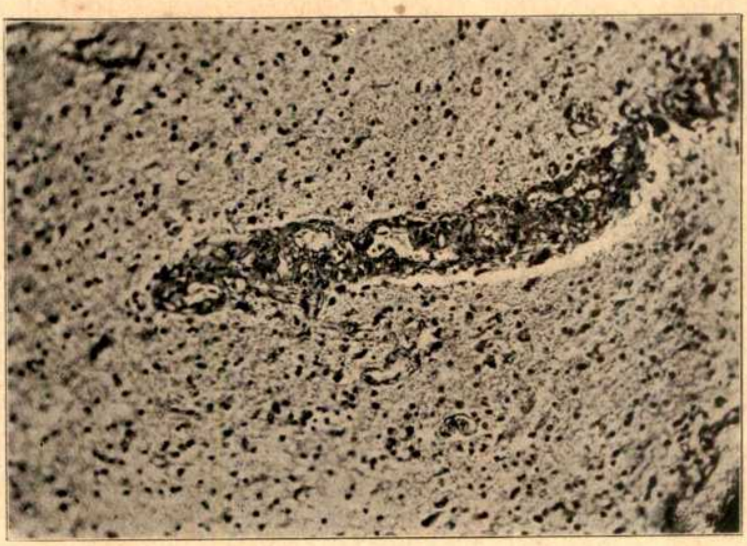

FIG. 25.—Case 11. A longitudinal section of a vessel, showing an extreme effect of endothelial proliferation.

Case 11.—H. B. (Dr. Tooth), a large glioma of the right centrum ovale. The patient died seven years after the first symptom. (Figs 24 and 25.)

In places (fig. 24) the angioma formation only is seen. In others the intimal proliferation is very striking (fig. 25). A similar instance is taken from Case 6 (fig. 26).

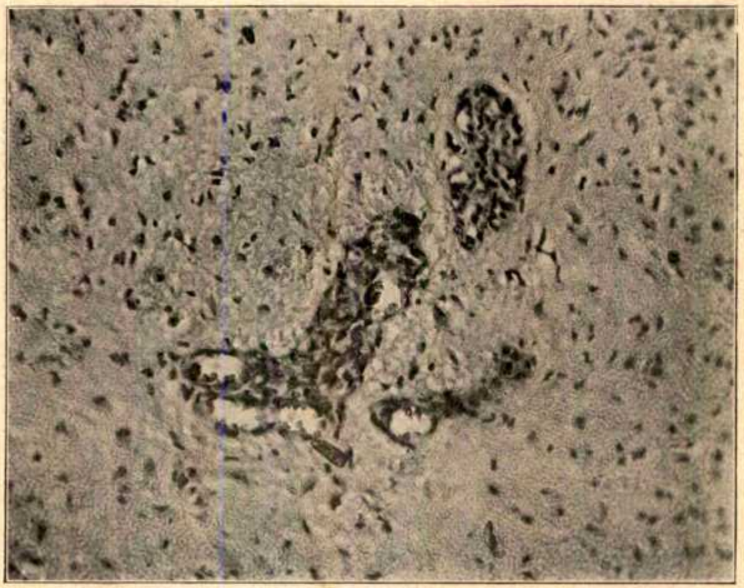

FIG. 26.—Case 6 (*vide supra*). A longitudinal and almost transverse section of (?) the same vessel. Showing complete obstruction of the lumen.

The following illustrates some of the features of vascular change very well.

Case 12.—W.H., a man, aged 47 (Dr. Jackson). Two months before admission he fell on the back of his head and immediately after his left leg became weak and this progressed. The connexion between the blow and the onset is so obvious that one must suppose that the tumour was in existence in a latent form and that traumatic influences either woke up malignant activity or caused a small hæmorrhage. However that may be, the case ran a rapid course from this time, and a left hemiplegia with gross optic neuritis resulted. Two months after the first symptoms he came to operation and the arm-area was found involved in growth, a richly cellular glioma of ill-defined margin extending deeply to the lateral ventricle; as much as possible was removed. He made a good recovery, and all symptoms improved; hemiplegia less, and optic neuritis subsiding. He wrote four weeks after discharge that he was still improving, but I learn that he died later, ten months after the first symptom. (Figs. 27, 28, 29, 30, 31.)

Fig. 27 shows an intensely richly nuclear part of the growth; annulation marks its activity. Tiny vessels can be seen ramifying in all directions. They are quite primitive, little more than channels with a thin limiting membrane and no endothelium can be seen.

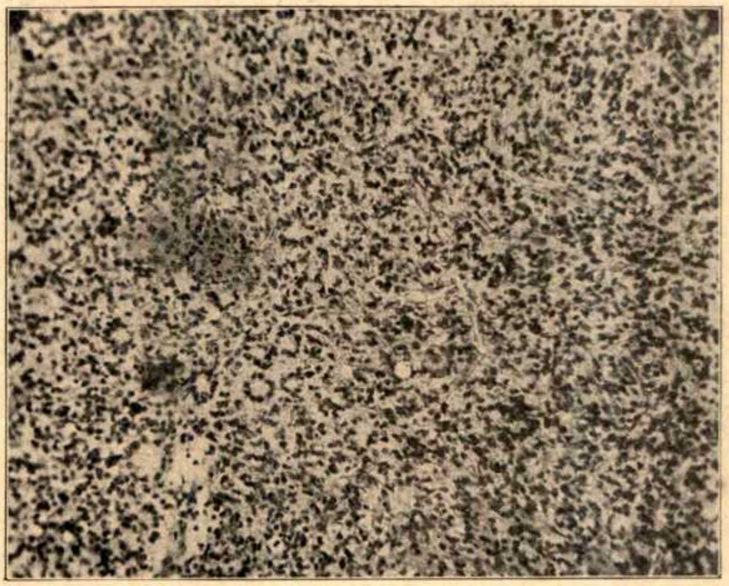

FIG. 27.—Case 12. From a highly active part of the growth. Fine vascular channels can be seen with a glass in the right central part of the field.

Fig. 28.—On the border of an area of necrosis; the small vessels are in great plenty, as indeed they are everywhere in all the sections, and the intimal proliferation can be seen in all degrees from the single layer of swollen cells to complete blocking of the lumen. The photograph is wanting in distinctness on this point.

Fig. 29 shows two bunches of vessels somewhat like a renal glomerulus. Some of the constituent vessels are pervious, and many are blocked.

Fig. 30.—In a necrosed area, a large vessel in the centre of the field, pervious, and containing blood corpuscles. Its wall presents a meshed appearance, which may be due to necrosis of proliferated intima, very much resembling on a small scale the structureless meshwork of a cholesteatoma. A neighbouring vessel appears to be thrombosed, full of fibrinous fibrils.

Fig. 31.—A vessel on the border of a necrosed area, probably containing organized thrombus.

In some of these pictures it is difficult to say how much the appearance is due to intimal proliferation—because the endothelium tends to degenerate with the other elements of the growth—and how much is due to organized clot. Both may be present; probably the sequence of events is—blocking of the smaller vessels which have an endothelial lining, by the multiplication of the cells composing it, and a subsequent thrombosis backwards to the larger vessels, and so starvation of blood to an area of the tumour.

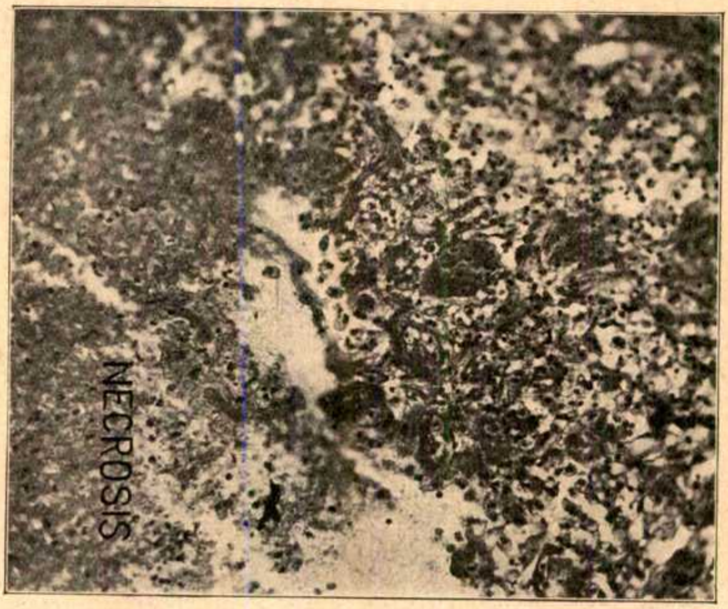

FIG. 28.—Case 12. Vessels on the border of an area of necrosis (left half of section). The central right half of the field shows a group of small vessels the endothelium of which is proliferated; but the photograph fails to bring out their features owing to obtrusion of other nuclear details.

Necrosis.—This brings us to the last stage in the life-history of the glioma—necrosis, a process which is going on *pari passu* with vigorous vitality elsewhere in the growth. Moreover, it is not too much to say that the more evidence existing in a given tumour of active growth, the more certainly will be found parts in which necrosis is in progress. Fig. 32 is a good picture of such an area taken from another case. There is an appearance of the calm of death about it—dissolution rather. The last remaining nuclei have still some chromatin, but it is fast disappearing; so they present a shrunken appearance very

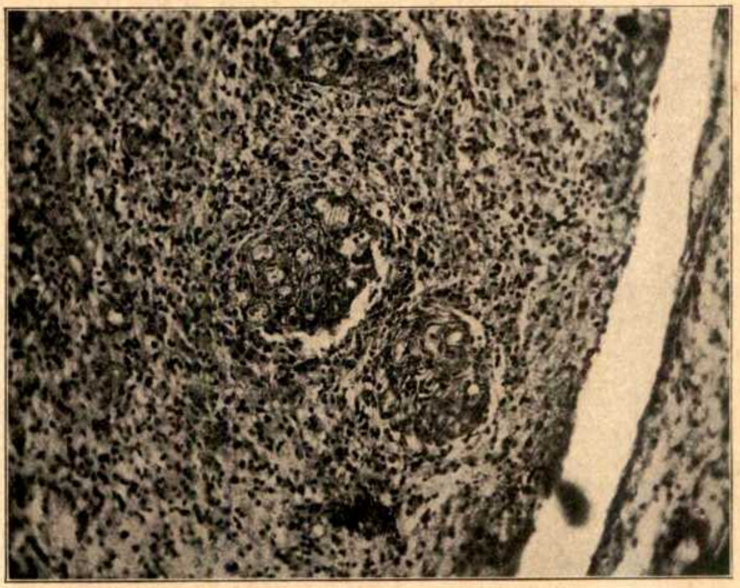

FIG. 29.—Case 12. Glomerular multiplication of vessels on the border of an area of necrosis.

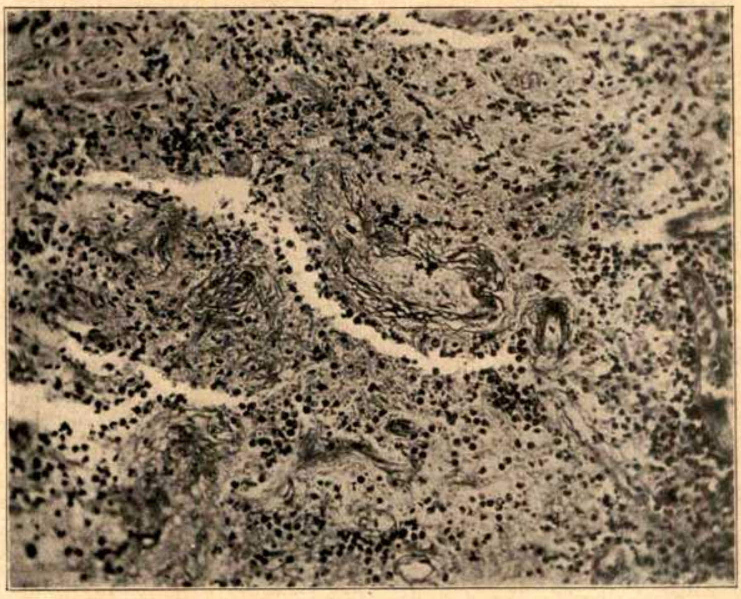

FIG. 30.—Case 12. In a necrosed area. In the centre of the field is a large vessel, pervious, containing blood. Its wall is meshed by degeneration. To the left is another in the same condition but probably thrombosed.

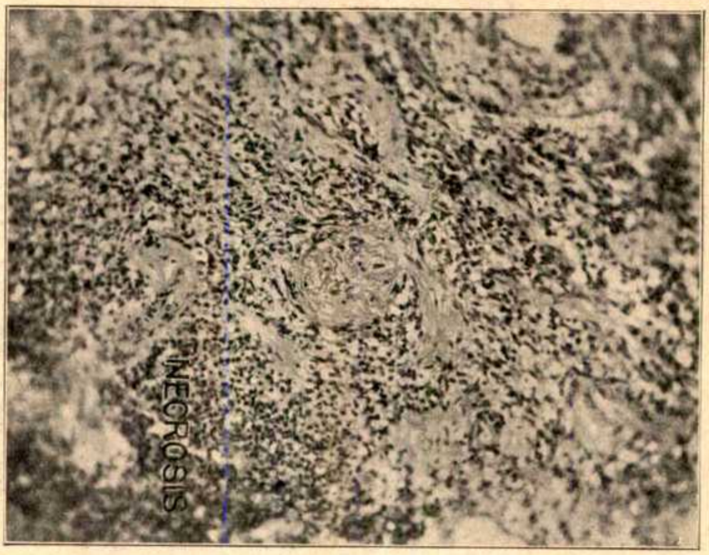

FIG. 31.—Case 12. A vessel on the border of a necrosed area. The appearance may be produced by organized thrombus.

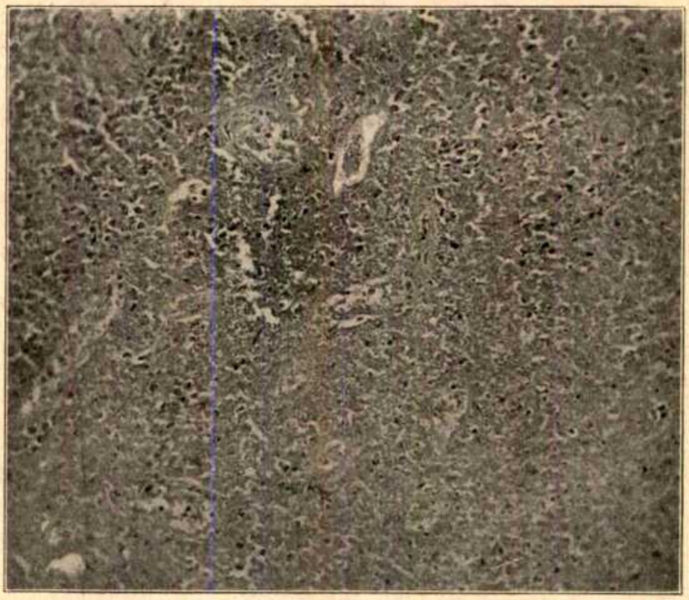

FIG. 32.—Necrosis. Granular amorphous ground substance with only a few nuclei remaining undergoing chromolysis.

different from the full, round bodies shown in so many of the active growths above. The rest of the field is made up of feebly staining amorphous débris, with here and there the remains of a blood-vessel also bearing evidence of decay.

Cyst formation.—The glioma shows the tendency to cyst formation perhaps more often than any other group. Pathologically this may be considered as a degenerative process, but clinically it may be as disastrous as the more malignant forms. Glioma cysts, which are sometimes single but more often multiple, may certainly be drained with temporary and even prolonged benefit, but it is doubtful whether the growth of the surrounding or underlying tumour, if of the active kind, is modified to any extent, and there is always the fear that by interference latency may awake to activity. This is, however, a risk that must be taken, in the event of operation disclosing an obvious cyst.

The simplest and earliest evidence of cystic tendency is shown in the rarefaction of the glia-stroma which may be seen in so many apparently innocent-looking growths. In its full development it presents a superficial resemblance to an emphysematous lung.

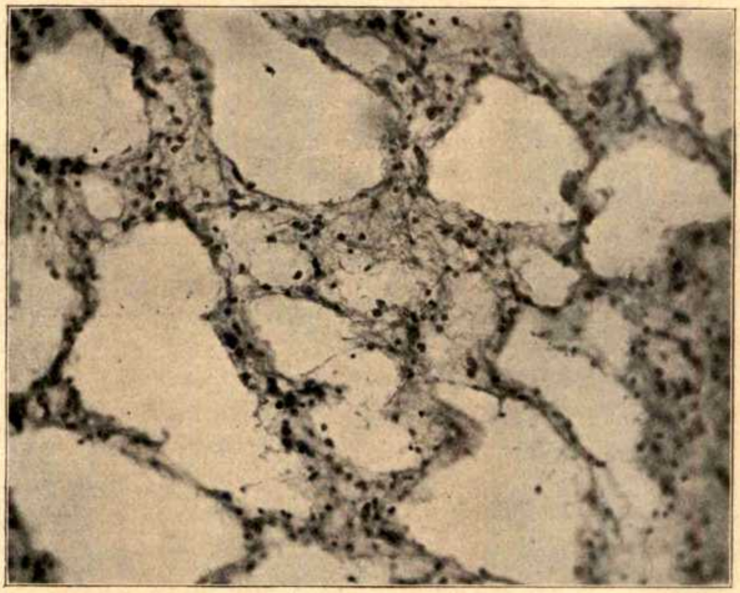

FIG. 33.—Case 13. Cyst formation, in a glioma of long duration. The glioma tissue presents no appearance of activity.

Case 13.—E. W. H., a man, aged 30 (Dr. Ormerod), gave a long history commencing with a fit, general convulsions, three years before admission, general drowsiness a year before that; but the fit has been reckoned as the first symptom—sixteen months, vomiting attacks, two months, weakness right leg. Vision: right, $\frac{6}{38}$; left, $\frac{6}{9}$. Consecutive atrophy of the right optic disk and intense neuritis of the left. A frontal growth of a quiescent type was suspected. He improved in hospital, and was discharged to report progress later. He died one year after. Dr. Stewart made a *post-mortem* examination outside, and found a large right frontal tumour and a small left frontal, one of the few multiple gliomata. (Fig. 33.)

Fig. 33.—The cysts occur in the midst of simple glioma structure and the section shows no evidence of malignity; but of course if cysts continue to enlarge by increase of their fluid contents, such a growth, however innocent pathologically, is clinically malignant from simple mechanical increase in bulk.

Cyst formation, in fact, would appear to be an evidence of long life, from the pathological standpoint, and the process rather one of atrophy than of activity.

In conclusion, it is evident that the glioma, when it enters upon an active stage, by the very exuberance of its activity carries on within itself a process of self-immolation. Also that this aspect of the question centres round the blood-vessels, which may increase vastly in number—an angiomatous stage; become blocked—an intimal proliferative stage; thrombosis spreads backwards into larger vessels—a thrombotic stage; and lastly there results necrosis of the area concerned. If this is the true sequence and proper interpretation there may be some hope of treatment in the future by some application of ultra rays after removal of the bone, such as has given results in some other vascular growths.

But this is only one side of the matter. The larger question still remains, how to meet the forces that are seething within the rapidly growing tumour. Complete recovery of the diffuse forms is practically impossible. One may almost assume that the earliest possible stage of growth, when the tumour might conceivably be removed completely, is undiagnosable in most parts of the brain. A removal as complete as possible seems to be followed by increased activity, and recurrence, or, worse still, a relatively latent growth, may be awakened into malignity. It seems that in the present state of our knowledge we must be content with relieving pressure by decompression in all gliomata, lest worse befall.

THE PATHS OF ENCEPHALIC INFECTION IN OTITIS.

BY CHRISTOPHER TYLOR, M.D.

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Introduction.

This paper has for its object the investigation of the various pathways by which infective processes, originating in the ear in the human subject, may reach the interior of the cranium.

The inquiry has been approached from the standpoint of the human morbid anatomist by a study of the *post-mortem* records of 644 cases of intracephalic infection, including 267 of infective diseases of the ear. Particular attention has been directed to those cases in which actual *post-mortem* examination has demonstrated the origin and spread of infection, or in which the infective processes had been observed during life in the course of operative procedures.

In a survey of the *post-mortem* examination records of St. Bartholomew's Hospital during the last fourteen years, namely, from October 1895, to October, 1909, the total number of cases in which infective middle-ear disease occurred was found to be 267 (collected from both medical and surgical *post-mortem* registers). The importance of infective disease of the ear as a cause of intracranial suppuration has long been recognized, and in the series of cases collected for the purposes of this inquiry it was found that leptomeningitis, including the tuberculous form, accounted for a fatal termination in 644 cases, and of these middle-ear disease was present in 129 cases, that is, in 20·03 per cent.

It is only in recent years that the importance of the labyrinth in relation to intracranial disease has been recognized. In a surprising number of this series of cases it will be shown that infection of the labyrinth has been the antecedent of meningeal or encephalic infection.

As we might expect, in records of the earlier cases, it is not always possible to ascertain the paths of infection owing to insufficient details in the *post-mortem* reports, yet, in a good many instances in which direct evidence was wanting, the path of infection could be inferred with considerable certainty. These doubtful cases have been noted and classified separately.

Among the more recent *post-mortem* examinations, histological examinations of the labyrinth have been undertaken, and these have revealed inflammatory disease in a number of cases where it had not been suspected to exist.

The chief forms of intracranial infections met with are:—

(1) Lateral sinus thrombosis.

(2) Brain abscess, including both cerebral and cerebellar abscess.

(3) The various forms of meningeal infection. Of this latter class the following varieties will be considered:—

(*a*) Pachymeningitis, in which the dura mater and, more especially, its external surface (pachymeningitis externa) is alone affected.

(*b*) Extradural abscess, in which a collection of pus forms between the dura mater and bone.

(*c*) Intradural abscess, in which the pus is situated between the dura mater and arachnoid, and is limited to one particular spot by adhesions between the membranes.

(*d*) Purulent leptomeningitis, in which pia and arachnoid membranes are chiefly involved—the purulent form generally affecting a large area of the brain—which is usually in a condition of encephalitis.

(*e*) Serous meningitis and internal hydrocephalus.

(*f*) Tuberculous meningitis concomitant with infective disease of the middle ear.

The investigation has been conducted with the object of ascertaining, first, the most common situations of the different intracranial lesions, and, secondly, the paths whereby the infective micro-organisms have been enabled to gain access to intracranial structures.

The pathology of the various morbid processes, as far as it concerns the subject of this paper, will be discussed, as well as certain anatomical features which have an important bearing upon the paths of encephalic infection.

§ 1.—*Bacteriology.*

Micro-organisms can readily make their way from the nasopharynx viâ the Eustachian tube to reach the tympanic cavity, in the mucous membrane of which they proceed to multiply and to produce their toxins. Acute otitis media is a common complication of those acute specific fevers in which sore throat is a prominent feature (of which scarlet fever is perhaps the best example), and in these cases infection reaches the ear through the Eustachian tube. In other cases, such as tubercle, infection may be carried to the ear by the blood-stream. Again, many cases of meningococcal cerebrospinal meningitis are associated with otitis media. What relation the infection of the ear bears to the meningitis in these cases we have yet to learn.

In only a comparatively few cases have the specific organisms concerned been recorded; in the majority of cases no bacteriological examination of the infective material appears to have been made. In forty-nine cases a bacteriological report on the nature of the infecting micro-organism was given, and the results are set out in the following table :—

Organisms concerned in Forty-nine Cases of Infective Middle-ear Disease.

Source from which cultivations were made	Pneumo-cocci	Meningo-cocci	Staphylo-cocci	Strepto-cocci	Mixed infection diplo- and strepto-cocci
Pus in meningeal exudate	20	6	2	5	1
Blood	3	—	—	—	—
Pus in ear or mastoid	2	1	1	1	—
Pus from brain abscess	1	—	—	2	—
Pus from extradural abscess	2	—	—	—	1
Pus from labyrinth	—	—	—	1	—
Totals	28	7	3	9	2

From the above table it will be seen that in the forty-nine cases in which a report on the nature of the infecting organism was made, the pneumococcus occurred in more than half, viz., twenty-eight; streptococci were responsible for nine, and meningococci for seven.

Bacteriological examination of the pus contained in the tympanum, or in those intracranial lesions secondary to ear-disease in cases of chronic infective otitis media for the purpose of ascertaining the organism primarily responsible for the disease, is of little value since the pus is almost certain to be contaminated by one or more organisms which have given rise to a secondary infection. The only satisfactory way of isolating the infecting organism is to examine bacteriologically the fluid from the tympanic cavity, obtained by aseptic puncture of the bulging tympanic membrane in the early stages of acute otitis media, or by examining the pus in acute mastoid abscess.

West [15], in the *St. Bartholomew's Hospital Reports*, gives the results obtained by him in an investigation conducted for the purpose of determining the organisms primarily concerned in the production of acute otitis media and consecutive suppurative mastoiditis. In cultivations made from the pus in thirteen cases, he obtained a pure growth of streptococci in nine, and of pneumococci in four instances. He points out, however, that in cases in which otorrhœa has existed for some time, and also in cases of meningitis, lateral sinus thrombosis and extradural abscess complicating a long-standing aural discharge, a pure streptococcal culture may often be obtained while the aural discharge is full of saprophytic organisms and *Bacillus coli.* He collected from the literature 100 cases of primary acute otitis media in which the bacteriological examination was trustworthy, and of these: 48 were pneumococcal, 27 were streptococcal, and 25 were staphylococcal; also 115 cases of acute suppurative mastoiditis, in which 74 were streptococcal, 34 were pneumococcal, and 7 were staphylococcal. These figures show that the infecting organism in cases of acute otitis media and mastoiditis is, in the great majority of instances, either some form of streptococcus or else the pneumococcus.

In the nine cases of middle-ear disease complicating diphtheria and typhoid fever no report on the organism present in the ear was apparently made, but in one case, associated with parotid abscess, the ear discharge contained diphtheria bacilli as well as staphylococci.

The presence of tubercle bacilli was demonstrated in two of the cases of tuberculous otitis media, but no bacteriological examination was made in the other cases.

The micro-organisms, therefore, which appear to be of chief importance in connexion with otitis media and its cerebral complications, are those which grow in long or short chains, namely, the streptococci and the pneumococci, and not those which grow in clumps, such as the staphylococci. It seems probable that the mode of growth and chain formation of the former class favours extension along minute channels, vascular or otherwise, and this may be the explanation of the frequency with which this form of organism is associated with infective otitis media and its cerebral complications.

§ 2.—*Anatomical Considerations.*

The following communications of the tympanum, mastoid antrum and cells with surrounding structures are of importance:—

(1) The petrosquamous fissure, which runs along the whole length of the tegmen tympani, and which may remain patent for a varying number of years after birth.

(2) Mastosquamosal fissure which is marked by numerous foramina when ossified.

(3) Fossa subarcuata. This is a large opening in the cerebellar surface of the petrous bone, which in childhood transmits a process of dura mater containing a vein which terminates in cells beneath the superior semicircular canal. This process may persist as a strand of connective tissue, and a case has been reported [8], which will be mentioned later, where infection of the labyrinth took place by this path.

(4) Lateral and sigmoid sinus, by means of numerous minute veins.

(5) Superior petrosal sinus, by means of a small vein.

(6) Inferior petrosal sinus, by a vein from the labyrinth.

(7) Free communication through the bone with the duramatral system of veins.

(8) Jugular fossa, the root of which is pierced by a number of veins draining the floor of the tympanum.

The relations of the aqueductus Fallopii, which lodges the facial nerve, to the boundaries of the tympanic cavity may be considered at this point. The Fallopian aqueduct first comes into relation with the inner wall of the tympanum, where it lies above the fenestra ovalis; posteriorly to this point it curves downwards along the posterior wall. On the posterior tympanic wall is the pyramid which lodges the stapedius muscle, the tendon of which emerges from the apex of this bony prominence to gain its point of attachment in the neck of the stapes. The cavity in the pyramid is prolonged into a minute canal which communicates with the aqueductus Fallopii, and transmits the tympanic branch of the facial nerve which supplies the stapedius muscle. Here, it will be seen, is a direct communication from the tympanic cavity to the interior of the aqueductus Fallopii, and this may possibly serve as a path by which infective micro-organisms may reach the sheath of the facial nerve. The bony walls of the canal are imperfectly ossified until some years after birth, and even when ossification has occurred congenital gaps in the bone are liable to persist. It is well known that children are relatively more liable to facial paralysis than adults during the course of an acute or chronic middle-ear suppuration; and this is explained by the fact that in these cases ossification is incomplete. Again, a special characteristic of tuberculous otitis media is the early destruction of bone, and facial paralysis is comparatively frequent in association with these tuberculous cases. Schwabach, indeed, considers that facial paralysis is eighteen times more frequent in tuberculous otitis media than in other forms.

Blood supply.—Arterial blood is brought to the internal ear by a branch of the basilar artery which enters the labyrinth along with the auditory nerve through the internal auditory meatus, while the middle ear is supplied chiefly by branches of the external carotid. Minute vessels perforate the bone at numerous points, and in many cases infection spreads by means of a septic thrombus originating in one of them. They run in the mucous membrane, and so are in close relation to pathogenic processes taking place in the interior of the ear. The veins empty into the lateral sinus and veins of the dura mater, and into a venous plexus round the Eustachian tube. In connexion with the blood supply of the labyrinth, some important communications with the tympanum and the surrounding structures are described by recent authorities on the subject.

(1) The blood-vessels of the tympanic mucosa send minute branches into the bony wall of the promontory.

(2) The blood-vessels of the dura mater penetrate an area between the semicircular canals at the fossa subarcuata.

(3) The blood-vessels of the temporal bone surrounding the labyrinth communicate with the vessels in its capsule.

Shambaugh [12], in a paper entitled "Relations in the Blood Supply of the Inner Ear," published the results of an investigation made by him as to the channel or channels by which venous blood leaves the internal ear, and also as to whether communications exist between the blood-vessels of the tympanic mucosa and those of the membranous labyrinth and endosteum. In his paper he also gives the results arrived at by two different observers, Siebenmann and Eicher, in an investigation as to the first point, which are as follows:—

Siebenmann gives three channels by which venous blood leaves the internal ear, namely:—

(1) A vein in the internal meatus drained the blood from part of the cochlea.

(2) A vein along the aqueductus cochleæ drained the blood from the cochlea as well as the vestibule.

(3) A vein along the aqueductus vestibuli drained the semicircular canals and vestibule.

Eicher found only the second and third routes, while Shambaugh, in the pig, sheep, and calf found only the vein running along the aqueduct of the cochlea.

With regard to the second point, Shambaugh quotes Alexander on the communications between blood-vessels of the internal and middle ear, while he himself demonstrated that the branches of the labyrinthine artery, supplying the endosteum, penetrate the bony capsule at several points about the base of the cochlea and the vestibule, and that, apparently, in the ears of the calf at least, communications do exist between the blood-vessels of the tympanic mucosa and those of the membranous labyrinth and endosteum. If this is the case, it is possible that pathogenic organisms from the middle ear might infect the labyrinth through the medium of the blood-vessels.

§ 3.—*Pathological Considerations.*

As the result of infective disease in the middle ear, certain changes occur which give rise to alterations in the normal appearance of the various structures comprising the middle and internal ears. In the earlier stage of acute otitis media the vessels of the tympanic membrane become injected and reddened. Inflammatory exudation into the interior of the tympanum causes bulging of the tympanic membrane. Occasionally the membrane appears to be unusually resistant to ulceration and rupture; in these cases perforation is apt to be considerably delayed, and when it does occur may be so small that efficient drainage of the tympanic cavity is prevented. The mucous membrane lining the various cavities of the ear also undergoes certain changes. First of all, the mucosa becomes swollen, and exudes serum, mucus, or blood; later on the inflammatory process extends to the deeper layers, and the exudation becomes purulent in character. When the disease becomes chronic, the superficial epithelium is lost, or exhibits metaplasia; the surface has a red and granular appearance. On this surface polypoid masses of exuberant granulation tissue may originate, and it is not uncommon to meet with these polypoid masses almost completely obliterating the lumen of the external auditory canal. The secondary tympanic membrane may also become involved in ulcerative processes, and may eventually be completely destroyed. As a result of these changes thickening, adhesions or scarring of the mucous membrane may occur.

The bony walls are also subject to the destructive action of the bacterial toxins, and in the course of chronic suppurative otitis media they first of all become thickened; later on, the infective process may lead to caries of the bone, in which condition its medulla is replaced by granulation tissue, more and more bone being destroyed until, eventually, perforation takes place, or necrosis, in which a small or large portion of the bone is completely cut off from its blood supply, with the result that death of that portion of the bone occurs, and a sequestrum is formed. These pathological processes are apt to affect the ossicles, and it is not uncommon to find them lying loose in the cavity of the tympanum.

The situations in which caries and necrosis appear to be most common are:—

(1) The mastoid region, most often in the outer wall or anterior wall.

(2) The roof or posterior wall of the mastoid antrum are often perforated or completely destroyed, with the result that infection of the meninges, lateral sinus or brain occurs.

(3) The inner tympanic and antral wall. Here small patches of caries may be present leading to labyrinthine fistulæ, thus opening up a path of infection into the labyrinth.

(4) The walls of the Fallopian aqueduct, which may be partially or completely destroyed, and the facial nerve left exposed.

§ 4.—*Intracranial Morbid Anatomy.*

This will be considered in the various sections which deal with the different intracranial lesions, but a few preliminary facts may be mentioned at this point in order to avoid repetition in the following pages.

The dura mater is composed of tough fibrous tissue which is, in addition, often thickened by disease, and thus is enabled to offer a firm resistance to the passage of pathogenic micro-organisms through its substance.

In many cases of temporosphenoidal abscess perforation of the dura does occur, especially when the brain abscess is associated with an extradural collection of pus. It is not necessary, however, that perforation of the dura should precede infection of the pia and arachnoid membranes. MacEwan [9] considers the sequence of events which takes place in general meningeal infection, without perforation, to be as follows: When the bone is involved there is found on the visceral side of the dura a projection of granulation tissue, generally somewhat conical in shape, corresponding to the area of the bone affected. This gives rise to an indentation of the surface of the brain which causes the pia mater to become adherent to it. In this way the vessels of the pia mater may become directly infected from the primary focus in the ear without the dura mater being perforated. Owing to the pia mater being an exceedingly vascular structure, the infecting organism may be distributed by means of the vessels over a large area of the meninges, giving rise to a generalized suppurative leptomeningitis. Moreover, the pia mater gives off from its inner surface numerous minute vessels which extend perpendicularly downwards into the cerebral substance. This vascular arrangement, therefore, also favours extension of the morbid process to the interior of the brain.

When extension of the disease takes place into the lateral sulcus, the outer wall of the sinus becomes the seat of granulation tissue formation, which affords a natural protection against further infection of the sinus for the time being. Should the primary cause not be removed, either by natural arrest of the infective process or as a result of operative measures, sooner or later pathogenic organisms make their way through the sinus wall, giving rise to an endophlebitis. The inner wall becomes roughened and a deposit of fibrin takes place; this, by the deposition of successive layers, results in the formation of a thrombus, and the disease spreads along the sinus wall by continuity or by means of the anastomosing lymph spaces. Eventually the lumen of the vessel becomes blocked and a complete thrombosis is established.

In the case of infection of the sinus taking place from one of its small tributary veins, part of the clot within the latter projects into the lumen of the sinus and thrombosis in the latter takes place from this point.

If the primary disease be removed further infection of the thrombus may be prevented, if not disorganization of the thrombus occurs, and it commences to break down and to form pus, which is then carried to various parts of the body, with, of course, the production of pyogenic abscesses. Should the inferior portion of the sinus be blocked by the thrombus it is possible for the thrombosis to extend backwards to the torcular Herophili, and so to the opposite lateral sinus.

Abscesses of the brain are usually met with in the white matter, and this is due to the fact that the cortex, owing to its vascularity, is capable of offering an effective resistance to the destructive powers of the bacterial toxins. Moreover, the piamatral vessels extend perpendicularly downwards into the grey substance where they terminate in minute capillaries. Infective emboli are carried to these terminal portions and form a nidus around which the destructive processes may extend.

CHAPTER I.—LATERAL SINUS THROMBOSIS.

This complication was present in 55 of the total number of cases with infective disease of the middle ear, this being a percentage of 20·5.

Males were more liable to thrombosis of the lateral sinus than females, in the proportion of 33 of the former to 22 of the latter.

Lateral sinus thrombosis was of most frequent occurrence between the ages of 11 and 20, this decade contributing 21 cases, or 38 per cent. of the total number; while there were 13 cases, or 23·6 per cent. between the ages of 1 and 10. Only one case under the age of 1 year occurred, the youngest subject being aged 9 months. This case is of interest owing to the fact that it is uncommon for thrombosis of the lateral sinus to occur at such an early period of life. In no other decade did the cases exceed six in number. The oldest case noted was 60 years of age.

Lateral sinus thrombosis occurred in four out of the 31 cases of acute otitis media.

Some observers state that the right lateral sinus is more commonly affected than the left. In this series of cases this difference in favour of the right side was not appreciable, the right side being affected in 24, and the left in 23 instances. In six cases the disease was bilateral.

Analysis of Cases.

The majority of the 55 cases collected arose from spread of the disease into the sigmoid groove, and of these 18 were associated with extradural abscess.

Of the cases which belong to this class, 31 were produced by the disease involving the posterior tympanic wall or posterior wall of the antrum, or mastoid cells, and four through extension of the disease through the tegmen tympani.

In 13 there was either perforation or necrosis of the bony wall, infecting micro-organisms reaching the lateral sinus in this manner—while in 22 cases the bone was not affected. In 11 of the latter cases infection may have reached the sinus by direct contact of the latter with the bone separating it from the suppurating cavity, since these bony partitions are thin and it is quite possible for infection to take place in this way. It must be remembered, however, that these bony partitions are always perforated by small veins opening into the lateral sinus, and it is more than likely that in several of these cases infective phlebitis of one of the small veins was the origin of the sinus thrombosis.

Lateral sinus thrombosis is frequently associated with extradural abscess, but it is doubtful whether the latter can be considered to be the cause of the thrombosis in every case in which these two conditions are present together. The dura, as mentioned above, is a structure which is capable of prolonged resistance to the destructive action of bacteria and their toxins, and the micro-organisms have to penetrate two layers of the dura, namely, the endosteal and meningeal, before gaining access to the inner wall of the sinus. Moreover, it is not uncommon to find the dura covered by a layer of granulation tissue which forms one of the boundaries of a perisinus abscess, without symptoms of lateral sinus thrombosis being present. It is probable, therefore, that in some of these cases extension of the thrombotic process from a small venous tributary of the lateral sinus, and not the extradural abscess, was again responsible for thrombosis of the latter.

In eight cases out of the 55 the path of infection was through the small tributary veins of the lateral sinus. The proportion of cases originating in this way might seem to be a small one; it is a difficult matter, however, to demonstrate thrombosis of these small veins, and when we take into account the fact that thrombosis and infective phlebitis in them is bound to be of frequent occurrence in suppurative disease of the middle ear we must come to the conclusion that several cases included under the first heading more properly belong to the present class. Indeed, I think we may consider that the majority of cases of lateral sinus thrombosis originate in septic phlebitis and thrombosis of their small tributaries.

The two channels of infection, already mentioned, are responsible for most cases of sinus thrombosis.

Extension of the thrombotic process from a vein draining into the superior petrosal sinus, and from thence into the lateral sinus, was responsible for one case of the series. This path of infection appears to be comparatively rare. According to MacEwen, some of the labyrinthine veins drain into the inferior petrosal sinus, and therefore it might be possible for labyrinthine suppuration to be a cause of sinus thrombosis. No case of this kind occurred, and it would be difficult to demonstrate this path of infection, since suppuration in the middle-ear cavity in almost every case accompanies labyrinthine suppuration and the inferior petrosal sinus could, of course, be as readily infected from the former as from the latter.

Thrombosis in the jugular bulb and internal jugular vein, spreading upwards into the sigmoid sinus, occurred in one case. When the close relation of the jugular bulb to the floor of the tympanic cavity is considered, it might be expected that lateral sinus thrombosis due to this cause would be of comparatively frequent occurrence. These cases, however, appear to be rare; but if we bear in mind the fact that detection of a small thrombus in the jugular bulb is not an easy matter, even in a *post-mortem* examination, unless a special method is adopted, we must come to the conclusion that not a few cases are overlooked in which thrombosis in this situation has taken place. It is advisable, therefore, at the autopsy to examine the jugular bulb, not only in all cases of lateral sinus thrombosis, but also in those cases in which some form of general systemic infection has occurred without the lateral sinus being thrombosed. In order for the examination to be of any value it is necessary to resect that portion of the petrous bone which enters into the formation of the jugular fossa, special care being taken to remove a sufficiently wide area of bone, as well as the internal jugular vein. The walls of the vein and bulb can then be slit up and the lumen washed in a stream of water. In this way any roughening of their internal surfaces, indicating phlebitis, will be apparent.

In one case thrombosis spread from the lateral sinus of the opposite side, the thrombotic process extending backwards by the deposition of successive layers to reach the torcular Herophili and lateral sinus of the opposite side.

The question as to whether pyæmia can be caused by septic thrombosis of small veins in the bone, without the lateral sinus being affected, has been much discussed. In 24 cases of the present series, pyæmic, or septicæmic processes took place in various parts of the body, without the lateral sinus being thrombosed, and there seems to be no valid reason why general septic infection should not occur from this cause. It is well known that acute infective osteomyelitis, of the tibia for example, may give rise to pyæmia through involvement of the smaller vessels, and therefore it is only reasonable to suppose that infective osteomyelitis of the petrous bone, with the accompanying thrombosis of its vessels, should be able to bring about a similar result. On the other hand, as already mentioned, it is very easy to overlook a small mural thrombus in the jugular bulb, which would be quite sufficient to give rise to a general systemic infection.

Cases have been reported [7] in which observers have made the most careful *post-mortem* examination and have come to the conclusion that general infection has occurred from osteomyelitis of the temporal bone with its accompanying venous thrombosis. It is not probable that in all the 24 cases noted in this paper this was the mode of infection, but I think that we may assume that some cases at least were due to minute venous thrombosis, and not to thrombosis of the lateral sinus.

In this connexion the subject of pyrexia in children, unaccompanied by physical signs pointing to a definite lesion in some particular part of the body, may not be out of place.

We may be at times considerably puzzled to account for rise of temperature in children in whom, though they are obviously ill, there are no definite signs upon which to base a diagnosis. I can recall several cases of this kind in the wards of St. Bartholomew's Hospital, in more than one of which meningitis was first suspected. In one or two cases disease of the ear was found to be the cause of the pyrexia, but in others no definite diagnosis could be arrived at, and in course of time the temperature fell to normal and the child rapidly improved in health. In some cases attention is directed to the ear by the child constantly raising its hand to the affected side, and in these cases tenderness on pressure being made, either over the mastoid process or directly inwards over the tragus, is elicited. In others there is nothing to direct attention to the ear as being the source of the trouble. I would suggest that in a good many of these cases of pyrexia of doubtful origin in infants the cause lies in the middle ear. Micro-organisms of an infective nature reach the tympanic cavity viâ the Eustachian tube. Suppuration may or may not occur; in the former case perforation of the drum will probably occur, in which event the pus escapes by the external auditory meatus and the diagnosis becomes obvious; in the latter the infective process may extend to the numerous small veins which lie in the mucous membrane, and thus an absorption of the septic material into the systemic circulation takes place with its accompanying rise of temperature. It is probable that some cases of septic broncho-pneumonia arise in this way. Jacobi [6], in a paper on "Otitis Media in Children," discusses the question of septic absorption. His view is that in the young the lymphatic vessels are very active, and especially so in emaciated and atrophic subjects. In the presence of ear disease the epithelium lining the drum membrane and interior of the tympanum is often destroyed, thus permitting of more rapid absorption. These facts would explain the readiness with which absorption may take place from the interior of the ear into the lymph and blood circulation and lead to deposit in distant organs, with mild or serious sepsis or persistent elevation of temperature without obvious cause.

The paths of infection in the 55 cases of lateral sinus thrombosis are set out in the following table:—

I. Disease spreading into the sulcus lateralis		35 cases
(*a*) With extradural abscess	supra-tegminal	4 ,,
	perisinus	14 ,,
(*b*) Without extradural abscess— through posterior surface of petrous bone, mastoid cells or antrum	? by direct contact	11 ,,
	with perforation of bone	6 ,,
II. Thrombosis of small veins extending into the lateral sinus		9 ,,
III. Thrombosis in internal jugular vein or bulb spreading upwards		1 ,,
IV. Extension of thrombosis from sinus of opposite side		1 ,,

There were nine cases in which the path of infection was doubtful. These are not included in the above list. It will be seen that the first class of case appears to be by far the most frequent, but, as has already been pointed out, a good many of the cases in this class might be more properly grouped under the second division.

In connexion, therefore, with this form of intracranial affection, I should wish to direct attention to the following points:—

First, the probability that, owing to their anatomical arrangement, the small venous tributaries of the lateral sinus are the most important factors in the production of lateral sinus thrombosis, and that thrombosis in them is responsible for the majority of cases.

Secondly, that with regard to the frequent association of extradural abscess with thrombosis of the lateral sinus, it is doubtful if the presence of an extradural (perisinus) collection of pus is always an indication that thrombosis has occurred from extension of the micro-organisms contained in the former into the wall of the latter. In the majority of cases, no doubt, this has taken place, but there remain a few in which the thrombosis has an origin independent of the extradural abscess.

And thirdly, that general sytemic infection can and does occur, without thrombosis of the lateral sinus, from an infective osteomyelitis of the temporal bone.

CHAPTER II.—BRAIN ABSCESS.

Ear disease is responsible for about 35 per cent. of all cases of brain abscess; some observers, indeed, consider the proportion to be as high as 50 per cent.

Opinions differ as to whether temporo-sphenoidal abscess is more frequent than the cerebellar variety. Körner considers that the former is more common than the latter in the proportion of 63 per cent. to 31 per cent. Ballance, on the other hand, holds the opinion that cerebellar abscess occurs more frequently.

In this series of 42 cases of brain abscess, there were 30 of the temporo-sphenoidal to 12 of the cerebellar variety, or 71·4 per cent. of the former to 28·6 per cent. of the latter.

Taking both classes together the numbers appear to show that males are more liable to abscess of the brain of otitic origin than females, there being 28 cases in the male sex to 14 in the female.

In the present series of cases cerebral abscess was most common between the ages of 11 to 30, for 17 out of the 30 cases occurred in this period of life. The youngest subject was aged 6 months and was the only case under the age of 1 year. The oldest case noted was aged 45.

Out of the 12 cases of cerebellar abscess collected 8 were between the ages of 3½ and 30. No case occurred under the age of 3½, and the oldest case was in a subject aged 63. The cases of cerebellar abscess, however, are too few in number for much importance to be attached to these figures. It is, of course, most common to find temporosphenoidal and cerebellar abscesses as a result of infective middle-ear disease, but in a few cases the abscess may be situated in other parts of the brain. In these cases the infecting organism is carried by the blood-stream and the abscess is either the result of a general systemic infection, and is of a pyæmic nature, or of a simple transference from the primary disease in the ear by the local blood-vessels.

The other parts of the brain in which abscesses occurred were: the frontal lobe in three cases, the occipital lobe in two, and the parietal lobe in one case. With the exception of the two cases of occipital abscess, they were associated with either a temporosphenoidal or a cerebellar abscess and have not been included in the list of 42 cases of brain abscess.

The abscess may be acute or chronic, the latter variety being the more common. In the acute form the pathogenic organism is either of an especially virulent nature or the patient's powers of resistance are not so effective as they should be. If the lesion be chronic the surrounding brain matter is protected by the formation of a pyogenic membrane which limits the action of the toxic material. It is possible for a chronic abscess, thus encapsuled, to be present in the brain for a considerable length of time without causing any symptoms which might point to its existence. Usually, however, secondary infection of the abscess takes place, and if the organism responsible for it is of a virulent nature the chronic process may be transformed into an acute one, and the protecting capsule destroyed.

In the acute variety the walls are usually ragged and friable, while in the chronic form the walls are smooth and thick.

As far as can be ascertained from the *post-mortem* records, ten cases, including those of the pyæmic variety, were definitely acute, while six cases had thick abscess walls and were evidently chronic. In the remaining cases it was not possible to come to a definite conclusion as to whether the abscess was acute or chronic, though the majority of cases were most probably of a chronic nature. The contents usually consisted of greenish offensive pus; in one case of a tuberculous nature the contents consisted of caseous material, and one of the acute abscesses contained tarry, black, purulent material.

Condition of surrounding structures.—In cases of temporosphenoidal abscess the brain and its membranes were often adherent to the petrous bone, and in several cases a fistulous track led from the dura mater over the temporal bone into the abscess cavity. In other cases the pia mater and arachnoid were thickened and opaque and adherent to the brain. The brain matter in the neighbourhood of the abscess was often discoloured and softened, and in one case appeared to be undergoing a process of fatty degeneration.

Course and termination of an abscess.—The abscess may become chronic; if not, unless the collection of pus is drained by operation or drains itself through the external auditory meatus, it may burst into the lateral ventricle with a rapidly fatal result to the patient, or into the subdural space, setting up a leptomeningitis which is also rapidly fatal, or it may cause death, owing to its large size or unfavourable situation, by pressure on the vital centres in the medulla.

§ 1.—*Cerebral Abscess.*

When this occurs as a result of infection from the middle ear, its situation is almost invariably in the temporosphenoidal lobe, owing to the close relation of the latter to the roof and posterior wall of the tympanum. Twenty-nine out of the thirty cases collected occurred in this lobe of the brain.

The following were the paths of infection in the thirty cases of cerebral abscess :—

(1) Infection through the tegmen tympani.

(2) Infection through the mastoid antrum, cells, or posterior tympanic wall.

(3) Infection through vascular channels.

(4) Formation of the abscess as a result of general systemic infection. The infective material is carried from the ear by the blood-stream, and conveyed by it to various parts of the body. Finally, it reaches the cerebral circulation, and is arrested in one of the minute arterioles, with the result that a pyæmic abscess is formed.

The first two channels of infection may be considered together. Of the thirty cases of cerebral abscess, infection through the tegmen tympani was responsible for twelve cases; while in five, extension of pathogenic micro-organisms took place through the posterior tympanic wall, mastoid cells, or antrum. In these two classes extradural abscess was present on seven occasions.

Condition of the bone.—Perforation took place in five cases, while in seven, although there was no actual perforation, necrosis of the bone was present.

Extradural abscess appears to be frequently associated with temporosphenoidal abscess of otitic origin. In most cases there is a track of caries through which pus has made its way, from the seat of the primary disease, to infect the meninges, with or without the formation of an extradural abscess. The dura mater, however, is a structure very resistant to the destructive action of pathogenic bacteria, and the probability is that an abscess will form. If this is not evacuated, either by natural means, in which case the pus makes its way through the diseased portion of bone with drainage through the external auditory meatus, or by operation, sooner or later the pus will make its way through the dura to reach and infect the arachnoid and pia mater. It is not necessary, however, as has been pointed out, that there should be an extradural collection of pus, or that it should make its way through the dura for the interior of the brain to be affected with the formation of an abscess, for a localized pachymeningitis externa causes a bud of granulation tissue to project from the visceral surface of the dura. This projection gives rise to an indentation on the surface of the brain, causing the pia mater and arachnoid to adhere to the brain substance as well as the dura, with the result that infection can reach the latter through the vessels of the pia mater which send branches into the white matter.

Superficial abscesses in the cortex of the brain appear to be seldom met with, and this is probably due to the fact that the cortex, owing to its vascularity, is very resistant to the destructive action of bacterial toxins, and also to the fact that the blood-vessels afford an easier means of access into the white than the grey matter.

Condition of the dura mater.—In three cases it was thickened (pachymeningitis) and adherent to the brain, while in two cases it was covered with granulation tissue, and in a necrotic condition. It is probable that, in these cases, extension of the morbid process to the interior of the brain took place in the manner described above. In six of the seven cases associated with extradural abscess, the dura mater was perforated, and a fistulous track led from the abscess cavity into the interior of the brain. The dura mater was unaltered in one case.

Infection spread through the medium of vascular channels in four cases. Cases in which the cerebral substance external to the abscess cavity appears healthy in all probability originate in this way, but it must be remembered that the grey matter has great powers of recovery from the effects of disease, and it is possible that, in some cases where no fistulous track is evident, the line of communication with the exterior of the brain has been obliterated.

The veins which run in the mucous membrane lining the cavity of the middle ear drain partly into the veins of the dura mater, and an infective thrombus originating in one of the veins of the tympanic mucosa may reach one of the dural veins; the latter infects one of the piamatral system, and from this point the process can extend into the interior of the brain.

In some instances branches of the cerebral arteries which supply the temporal bone may become thrombosed, and minute infective emboli carried into their terminal branches in the white matter, thus forming a nidus around which pathological processes extend, giving rise to a cerebral abscess.

The perivascular lymphatics also are sometimes responsible for a similar result, especially when the original disease in the ear is of a tuberculous nature.

The fourth group of cases is that in which the abscess is a result of general systemic infection, with the formation of metastatic deposits of infective material in the interior of the brain. These abscesses are said to occur most commonly in those parts of the brain which derive their blood supply from the sylvian artery of the left side, and also in those parts which are situated at the base. I have been unable to collect any cases either in support or disproof of this view.

In one case of the series the brain abscess was purely pyæmic in character, though in three other cases a pyæmic abscess was present in addition to one of direct otitic origin.

One of the remaining cases was most probably due to an exploratory puncture of the brain at a previous operation; in the other seven I could not come to any conclusion as to the path of infection, owing to insufficient details being given in the *post-mortem* records.

The following table gives the varieties and frequency of the different paths of infection in thirty cases of cerebral abscess:—

I.	Infection	through	mastoid cells, antrum or posterior tympanic wall	5
II.	,,	,,	tegmen tympani	12
III.	,,	,,	vascular channels	4
IV.	,,	,,	exploratory puncture of the brain at a previous operation	1
V.	Pyæmic			1
	Doubtful cases, not classified			7

These figures show that the path of infection, in most cases of temporosphenoidal abscess of otitic origin, is through the roof of the tympanum. The most rational method of treatment, therefore, to adopt in a case of this kind is to perform the radical mastoid operation with exposure of both cranial fossæ. Thus, if the sigmoid sinus is healthy, the temporosphenoidal lobe should be punctured directly upwards through the dura covering the tegmen. This method offers a very much better chance of finding the intracranial abscess than the operation, performed by some surgeons, of trephining the bone over that portion of the brain where the abscess is supposed to lie.

The above are the more common channels of infection, but one which is of interest, though it rarely occurs, may be mentioned: namely, that in which infection is conveyed by one of the various processes of dura mater which enter foramina in the temporal bone. Kümmel [8] reports a case in which this occurred. The process of dura mater concerned in this case was the one passing into the fossa subarcuata, to which attention has already been called. It was represented by a band of connective tissue extending from granulations in the mastoid, from which the infection originated, to the perforated area in the upper part of the petrous bone.

§ 2.—*Cerebellar Abscess.*

Twelve cases of this variety of abscess occurred and the paths of infection noted were:—

(1) Through the posterior tympanic wall, mastoid cells or antrum as a result of necrosis or perforation of the bone, with or without the formation of an extradural abscess.

(2) By infection spreading from the lateral sinus.

(3) By infection spreading from the labyrinth.

Group 1.—Four cases arose as a result of infection spreading in this manner, and of these, perforation or necrosis of the bone was present in three instances—and perisinus abscess also occurred in these three cases—while the fourth was the result of infection through the posterior tympanic wall without the formation of a perisinus abscess. This pathway of infection is similar to that which occurs in cerebral abscess and the same remarks therefore apply.

Group 2.—*Infection through the lateral sinus.*—Most cases of cerebellar abscess are in direct contact with the sigmoid sinus, and the way in which pathogenic organisms reach the cerebellum may be as follows: When the whole circumference of the sinus is involved and is the seat of infective organisms, the cerebellar veins may become infected and thrombosis result. By this means the bacteria which are responsible for the primary disease, or in some cases those which have brought about a secondary pyogenic infection, are conveyed to the interior of the cerebellum to form a nidus which is the starting point whence the bacterial toxins may commence their destructive processes. In other cases the dura mater may become thickened, in the way described under the section dealing with cerebral abscess, thus bringing the duramatral system of veins into communication with the veins of the pia mater.

Three cases were due to infection spreading from the lateral sinus, and in one of these the sinus was filled with greenish pus. Direct extension to the tentorium cerebelli took place, with the formation of a superficial abscess cavity in the cerebellum. This communicated by a track the size of a pin's head with a second deeper abscess in the lateral lobe.

Group 3.—Infection through the labyrinth is an important source of cerebellar abscess. In four out of the twelve cases collected the spread of infection took place through the internal ear. In three of these cases it occurred in young subjects—their ages being 3½, 4, and 19—while in the fourth case the age was not stated.

It is now recognized that infective disease of the labyrinth is responsible for many more cases of cerebellar abscess than was formerly thought to be the case, and that it is one of the more important, if not the most important, causes of abscess formation in the cerebellum. According to Okada a preponderating majority of cerebellar abscesses follows labyrinthine suppuration, and only a third are secondary to sinus disease. The subject of labyrinthine infection as a cause of encephalic suppuration will be more fully dealt with in the section dealing with meningeal affections of the brain; there the various points at which infection may gain entrance to the interior of the internal ear will be noted, as well as the paths whereby the infective organisms may leave it.

With regard to the actual manner in which infective micro-organisms reach the brain, in cases of cerebellar abscess due to infection from the labyrinth, the probable sequence of events is as follows: Pathogenic organisms leave the internal ear through the internal auditory meatus along the sheath of the eighth nerve. Infection of the meninges takes place, giving rise to a local pachymeningitis, and spreads from this point in the manner described above to the interior of the cerebellum.

It is possible for the cerebellum to be infected through the veins in the tympanic mucosa, in a similar manner to that described under cerebral abscess. No case of this kind occurred in the collected cases of cerebellar abscess.

Spratt [14] has described a case in which leptomeningitis occurred as a result of infection of the meninges by means of the sheath of the facial nerve. It would seem possible, therefore, that supposing in this case the infecting organisms had not been sufficiently virulent to produce a generalized leptomeningitis, or that the resisting power of the dura mater had been greater, local pachymeningitis might have resulted; in which case infection of the cerebellum, with the formation of an abscess in its substance, might have taken place. One would expect that, if this is a possible path of infection, children would be more liable to cerebellar abscess, for in early life the canal in which the facial nerve lies is imperfectly ossified, and it is well known that facial paralysis, resulting from infective disease of the middle ear, is relatively more common in children than in adults.

In tuberculous disease of the middle ear destruction of the bone is often early and very extensive, and facial paralysis is often an early symptom. One would expect, therefore, in these cases also, that, as infection of the facial nerve sheath is frequent, cerebellar abscess might result in a good number of cases. I have not been able to discover any case in which cerebellar abscess was caused in this way.

We may conclude, therefore, that although this path of infection may be possible, it is of very rare occurrence.

Another case was reported [13] in the *Archives of Otology* in which a cerebellar abscess was situated in the base of the cerebellum. Pus had tracked between the two tables of the temporal bone from the mastoid antrum and had thus infected the cerebellum. This is another rare pathway of infection in cerebellar abscess and need not be further considered.

TABLE OF PATHS OF INFECTION IN TWELVE CASES OF CEREBELLAR ABSCESS.

Mode of infection	Cases
Through posterior tympanic wall, mastoid cells or antrum	4
,, lateral sinus	3
,, labyrinth	4
Paths doubtful	1

No cases occurred in which the cerebellar abscess was due to infection through the vessels of the tympanic mucosa, or as general systemic infection with the formation of a metastatic abscess. These modes of infection, however, are of importance and probably occur almost as often as they do in cases of cerebral abscess.

CHAPTER III.—MENINGITIS AND EXTRA- AND INTRA-DURAL ABSCESS.

§ 1.—*Pachymeningitis.*

This term is applied to inflammation of the dura mater, and the inflammatory process may be simple or purulent. It most commonly affects the outer surface of the dura, in which case the condition is known as pachymeningitis externa. The internal or visceral layer may be affected as a result of the inflammation spreading through the meshes of the external layer, or in a few cases as a result of suppurative inflammation of the pia-arachnoid; the condition is then termed pachymeningitis interna. The inflammatory process may remain of a simple nature, but, if the primary cause be not removed, either by natural arrest of the ear disease or by operation, the simple inflammation may be transformed into a purulent one. If the pus formation continues the dura mater will be stripped from the bone to make room for the collection of pus, and an extradural abscess results.

I have collected twenty-five cases of otitic pachymeningitis exclusive of extradural abscess, in which the condition of the dura was noted. It is probable, however, that inflammatory changes of a slighter degree were present in many of the remaining cases. These, together with thirty-four cases of extradural abscess, illustrate the different degrees of pachymeningitis which may occur, varying from a simple infection of the dura to an extensive extradural abscess containing an ounce of pus.

The cases of pachymeningitis may be classified according to their pathological nature, as follows:—

(*A*) *Simple* (*non-purulent*).—The earlier stage of pachymeningitis observed was slight injection of the dura mater; in the next stage the inflammation was more marked, the dura being distinctly reddened and having a granular appearance, sometimes also being coated with lymph.

(*B*) *Adhesive.*—In this form there is the formation of a plastic exudate which binds the dura mater to the bone, pia-arachnoid, or to both bone and pia-arachnoid.

(*C*) *Purulent.*—In the early stage the dura is covered by a layer of granulation tissue from which exudes purulent lymph or actual pus. At a later stage of the purulent process pus collects between the dura and the bone, stripping off the latter from the former and giving rise to an extradural abscess.

(*D*) *Necrotic.*—In this form the proper blood supply of the dura mater is interfered with, or the infective organisms are especially virulent and the membrane becomes grey and sloughy, leading to—

(*E*) *The perforative form.*—The necrotic portion gives way and a perforation of varying size results.

(*F*) *Tuberculous.*—The most common variety observed was the adhesive form. The dura was adherent to the pia-arachnoid and brain in six cases, to the bone in two, and to both brain and bone in two cases.

A local pachymeningitis, by causing adhesions between the dura and pia-arachnoid, tends to prevent the spread of infective micro-organisms to the brain; should ulceration of the adherent membranes, however, take place, or should the simple process be transformed into a purulent one, infective phlebitis in the veins of the pia mater is likely to occur and a generalized leptomeningitis or brain abscess results.

The perforative form may set up a leptomeningitis, pathogenic organisms making their way into the intradural space.

Purulent pachymeningitis usually gives rise to an extradural abscess. Pachymeningitis also frequently accompanies lateral sinus thrombosis, and, in some cases, is responsible for the thrombosis.

Tuberculous pachymeningitis.—Two cases of this variety occurred. In one of them the dura was inflamed and its visceral surface covered with pus, infection having taken place through the petrous bone, which was extensively diseased; in the other there was coarse tuberculosis of the dura in the posterior fossa of the skull infiltrating the occipital lobe of the brain.

Condition of the bone.—The bone beneath the affected portion of the dura was often discoloured, sometimes even black. In some cases it was reddened and rough, in others it was carious and necrotic and its dural surface covered with granulation tissue. In other cases again there was perforation leading into the tympanum, mastoid antrum, or cells. Finally, the bone may be unaltered, in which case the dura mater has become infected, most probably as a result of the infective phlebitis of one of the veins of the tympanic mucosa extending into a vein of the dura mater.

§ 2.—*Extradural Abscess.*

This may be the result either of a purulent pachymeningitis, or of perforation of bone, in which case pus makes its way through the perforation to form an abscess beneath the dura mater, between it and the bone. This form of abscess was present in 34 out of the 267 fatal cases with infective ear-disease, and the positions in which the pus was situated were: Nineteen cases in the neighbourhood of the sulcus lateralis (12 of which were perisinus abscesses), 14 cases over the roof of the tympanum (suprategminal abscess) and 1 case at the apex of the petrous bone.

Abscess in neighbourhood of lateral sulcus.—The neighbourhood of the sulcus lateralis is the most common situation in which to find an extradural abscess, and infection appears to spread through the posterior tympanic wall in the great majority of cases. Thirteen cases arose in this way, five originated from the mastoid antrum or cells, while in one case infection appeared to have spread from the labyrinth vià the aqueductus vestibuli, and gave rise to an empyema of the saccus endolymphaticus. Many of these cases were associated with thrombosis of the lateral sinus and in one case the sinus wall was perforated. In this case it is probable that the lateral sinus thrombosis was the cause of the perisinus abscess. It is possible for a collection of pus within the sinus to be present together with a perisinus abscess and yet for the two to be independent of one another. In a case such as this the wall of the sinus will be deprived of its proper blood supply and will probably perforate, and the extra- and intra-venous collection of pus become a single abscess; so that when a collection of pus is discovered *post-mortem* within and around the sinus it is not always possible to tell whether the former is responsible for the latter or *vice versa*, or whether both arose from independent sources.

This form of extradural abscess may:—

(1) Discharge externally by perforation of the mastoid process, or through the foramen for the emissary vein, or through the mastoid antrum, or cells, and so through the external auditory meatus.

(2) Involve the lateral sinus.

(3) Set up a leptomeningitis in the posterior fossa.

(4) Give rise to a cerebellar abscess.

(5) Cause tempero-sphenoidal abscess by spreading upwards and anteriorly over the posterior edge of the petrous bone.

§ 3.—*Suprategminal Abscess.*

The roof of the tympanum as a site for an extradural abscess comes next in order of frequency. Suprategminal collections of pus are commonly associated with an abscess of the temporosphenoidal lobe of the brain, the latter often being adherent to the dura mater, forming the inner wall of the extradural abscess. It is common to find a perforation of the wall leading into a fistulous track communicating with the cerebral abscess cavity.

The pus may spread in the following directions:—

(1) Upwards, giving rise to a temporo-sphenoidal abscess.

(2) Backwards, over the posterior margin of the pars petrosa, forming a perisinus, in addition to a supra-tegminal, abscess.

(3) Outwards, along the superior surface of the petrous bone. It may terminate by perforating the tegmen tympani and draining into the tympanic cavity, or by bursting through the dura mater into the intradural space, setting up a diffuse leptomeningitis.

In one case the abscess was situated at the apex of the pars petrosa and was most probably of vascular origin. An extradural abscess may be situated around the carotid artery in the carotid canal. This situation, however, is a rare one, and no abscess of this kind occurred as a complication in any of the cases collected.

Condition of the bone.—In nine cases the bone was carious and necrotic, although not actually perforated; in five cases it was perforated, and in four cases it was unaltered. In the remaining sixteen cases no note was made as to the state of the bone. In the four cases in which the bone was unaffected and probably in several of the others, in which no note was made as to its condition, the pathway of infection was in all probability a vascular one, as in the case of pachymeningitis without abscess formation. These cases in which the bone is not carious or necrotic are of interest clinically, since they are often accompanied by frequent and severe rigors with high temperature, although there is no evidence that the lateral sinus is thrombosed. In these cases complete recovery may take place after drainage of the abscess without any exploration of the sinus or ligature of the internal jugular vein. On the other hand, in those cases of perisinus abscess in which the bony partition between the dura and the middle ear has been extensively destroyed the symptoms are often of a comparatively mild nature.

Condition of the dura mater forming the abscess wall.—The dura may be stripped from the bone over a considerable area, its endosteal surface may be reddened and covered with granulation tissue and fibrinous deposits if the abscess is acute; if of a more chronic nature it may have the appearance of a pyogenic membrane. In the later stages of the disease, or if a secondary infection occurs, the walls of the abscess may become sloughy and necrotic, and finally perforate; the perforation in these cases varying from the size of a pin's head to that of a sixpenny-piece. The size of the abscess varied from a minute one not much larger than a small pea, to one of considerable size containing an ounce of pus.

Pachymeningitis may be simple or purulent. If the former is of the adhesive variety the dura mater may become gummed to the bone and pia-arachnoid, and so to the brain by a plastic exudation. This matting together of the membranes forms a barrier which tends to prevent the passage of pathogenic organisms through it. Should the simple pachymeningitis, however, be converted into a purulent one this matting together of the dura- and pia-arachnoid affords a pathway of infection to the vessels of the pia mater directly from the ear.

There are two main pathways of infection, namely, through the bone or through some vascular channel, such as the small veins of the dura mater or the lateral sinus, but it is probable that infection spreading from the lateral sinus is a comparatively uncommon cause of pachymeningitis, since the veins of the tympanic mucosa are likely to be involved in many more cases than is the lateral sinus.

§ 4.—*Intradural Abscess.*

A localized collection of pus in the intradural space is known as an intradural abscess. I have only been able to find three cases of this form of abscess, two of which were situated in the posterior fossa of the skull, and the other in the middle fossa. In the first case, the abscess was lying in the meshes of the pia mater, over the base of the occipital lobe of the brain; in the second case, it was placed over the roof of the tympanum, and the bone in this position was carious and necrotic. The third case was due to a necrosis of the labyrinth and was situated on the under-surface of the cerebellum.

An abscess of this kind is usually secondary to an extradural collection of pus which has escaped through a perforation in the dura mater into a part of the intradural space which has been shut off from the general cavity by adhesions. The abscess may, however, be formed without any preceding extradural abscess, and such cases must have a vascular origin.

§ 5.—*Serous Meningitis.*

I have included under this heading those cases of infective otitis media which are accompanied by an increase in the normal amount of either the subarachnoid or ventricular fluid, or of both together. In thirty-six cases a definite increase in the subarachnoid or ventricular fluid was present, and in several of them the ventricles were greatly distended with a large excess of cerebrospinal fluid. The fluid was either quite clear or was slightly turbid. The cases have been classified according as to whether the excess of fluid was in the subarachnoid space or the ventricles, or both together, thus:—

(1) Meningitis serosa externa ... ... 8 cases.

The excess of fluid is confined to the subarachnoid space.

(2) Meningitis serosa interna ... ... 21 cases

In this variety the ventricles of the brain are alone affected. This condition is also known as internal hydrocephalus.

(3) Meningitis serosa externa et interna ... 7 cases.

In this variety there is excess of fluid in both ventricles and subarachnoid space.

It will be noticed that most cases appeared to be of the ventricular variety, but it is possible that some of these were also accompanied by an effusion into the subarachnoid space, and that the latter collection of fluid escaped during the process of extracting the brain from the skull, and so was overlooked.

Twenty-three of the cases were associated with a leptomeningitis, which was either chiefly or entirely limited to the base of the brain, and seven occurred in conjunction with a more generalized meningitis. Of the remaining six cases, two were associated with cerebellar abscess alone, and there was no evidence in these cases that the abscess was leaking—one with intradural abscess and lateral sinus thrombosis, one with perisinus and cerebellar abscesses; while the last occurred in a case of general tuberculosis without any intracranial complication being present. With regard to those cases which were associated with leptomeningitis—perisinus abscess was present as an additional complication in four cases, labyrinthitis in five, temporosphenoidal abscess in one, and a suprategminal extradural abscess in one case.

An increase in the normal amount of cerebrospinal fluid may occur in the course of infective disease of the middle ear, especially in the chronic variety; but it is stated to be more frequently present when labyrinthitis or perisinus abscess occurs as a complication (Barr). The effusion may be acute or chronic, and in some cases the serous fluid may collect so quickly as to produce pressure on the cerebral blood-vessels, ending in their occlusion, and the rapid death of the patient (meningitis serosa maligna). Occasionally the fluid may be limited by adhesions. In one case a localized leptomeningitis in the neighbourhood of the internal auditory meatus formed a cyst-like collection of fluid surrounding the intracranial portions of the seventh and eighth nerves.

Causation.—The pia mater is a vascular membrane, consisting of a minute plexus of blood-vessels held together by extremely fine areolar tissue. It invests the entire surface of the brain, dips down between the convolutions, and forms at the base of the brain the velum interpositum and choroid plexuses of the ventricles. These are formed by an ingrowth of the pia mater, and in the lateral ventricles they consist of the vascular-fringed borders of the velum interpositum. They communicate with each other at the foramen of Monro, and are prolonged backwards as far as the choroid plexuses of the third ventricle. Those of the fourth ventricle are formed by a similar process of pia mater, the tela choroidea inferior.

Owing to this arrangement of the pia-mater, inflammation, especially of its basal portion, can easily extend to the vessels of the choroid plexuses, and lead to an increased exudation of fluid into the ventricular cavities. Direct or indirect communications exist between the ventricles, and if these are not obliterated by adhesions, the fluid may spread to the other ventricles, and cause a general distension of the ventricular system.

In thirty out of the thirty-six cases a definite leptomeningitis, either simple or purulent, was present, and in twenty-three of the cases it was either confined entirely to the base, or else the base was more gravely affected than other parts of the brain. In the remaining six cases, five were associated with either extradural abscess, brain abscess, or lateral sinus thrombosis, and it is extremely likely that in these cases also there was a localized inflammation of the pia mater.

It is probable, therefore, that most cases of serous meningitis and nternal hydrocephalus are caused by an inflammation of the pia mater, especially if the inflammatory process is situated at the base of the brain.

In those cases in which the labyrinth is involved, inflammation may spread along the sheaths of the seventh and eighth nerves, and so reach the pia mater which forms the tela choroidea inferior, leading to a dilatation of the vessels of the choroid plexus in the fourth ventricle, and an increased output of fluid into that cavity; or possibly along the aqueduct of the vestibule into the intradural space, giving rise to an increased production of subarachnoid fluid.

Some cases, no doubt, are unassociated with any gross inflammatory changes in the serous membranes of the brain, and in such cases toxins produced in the ear and circulating in the blood may stimulate the membranes to hypersecretion. It has been suggested that the severe cerebral symptoms, such as headache and vomiting with pyrexia, which are occasionally observed during the course of a chronic middle-ear suppuration in children and young adults, may be due to mild attacks of serous meningitis.

There remain a few cases associated with infective ear disease, in which serous meningitis and œdema of the brain and its membranes may be due to lesions in other parts of the body, and not directly to the ear disease. It is well known that this condition sometimes occurs in extreme venous dilatation from obstruction, as in mitral stenosis; in Bright's disease also a similar condition is occasionally present.

We may conclude, therefore, that while in the great majority of cases serous meningitis and internal hydrocephalus are due to an inflammation of the pia mater, yet there are some cases in which there is no obvious lesion of that membrane. Cases such as these may be due to toxins circulating in the blood, and that a third group of cases may exist in which, although infective disease of the middle ear is present, the serous effusion is due to some other cause, such as venous obstruction or general toxæmia.

§ 6.—*Purulent Ventricular Meningitis.*

A collection of purulent fluid was found in the ventricles of the brain in fifteen cases. Of these, six were due to the rupture of a cerebral abscess into the ventricle. Of the remaining nine cases, five were associated with leptomeningitis alone, and four with leptomeningitis and some other intracranial complication, namely, temporosphenoidal abscess in two cases, and labyrinthitis and perisinus abscess in one case each.

A purulent inflammation of the pia-arachnoid membrane is probably responsible for those cases of purulent ventricular meningitis which are not due to the rupture of a cerebral abscess into the ventricle, and the mode of infection is probably similar to that which occurs in simple ventricular meningitis.

§ 7.—*Tuberculous Meningitis associated with Infective Otitis Media.*

I have collected all the cases of tuberculous meningitis upon which *post-mortem* examinations have been made at St. Bartholomew's Hospital during the last fourteen years, with the object of ascertaining, first, the proportion of tuberculous meningitis cases associated with tuberculous or other infective disease of the ear, and, secondly, whether the ear can be considered as the primary focus of infection in any considerable number of cases.

The total number of tuberculous meningitis cases upon which autopsies were held was 368, and of these thirty were associated with infective disease of the ear, this being a percentage of 8·1. Bilateral otorrhea was present in fifteen cases, so that the total number of ears affected was forty-five. It is probable that infective ear disease was present in other cases also, since in a good many instances the ears were not examined. In only one case of tuberculous meningitis was a histological examination of the labyrinth made, and this revealed bilateral labyrinthitis, secondary to the meningitis. It is also possible that, in some of the cases with bilateral disease of the ear associated with tuberculous meningitis, if the labyrinth had been examined it would have been found to be diseased.

In twenty-one of the thirty cases there was a definite focus of dissemination in other parts of the body, such as a breaking-down caseous lymphatic gland. There remain nine cases in which no focus, other than the ear was discovered.

In the series of 267 cases of infective otitis media, eight were of a tuberculous nature, and in the majority of them the destruction of bone was considerable. In five of them tuberculous meningitis occurred as a complication, and in four of the latter cases no obvious focus could be found in other parts of the body.

The cerebral blood-vessels are accompanied by perivascular lymphatics, while the pia mater itself is very rich in lymphatic vessels, and is therefore a particularly favourable structure for deposits of tuberculous material. Moreover, the stylomastoid artery, which is the main vessel of supply to the tympanic mucosa, anastomoses with the internal auditory artery which ramifies in the pia mater at the base of the brain. This anatomical arrangement, therefore, favours the spread of tubercle bacilli from the tympanum to the pia mater.

Three cases occurred in which infection by spreading along the lymphatics caused tuberculous intracranial lesions. In one of them there was coarse tubercle of the dura in the posterior fossa, in the second a tuberculous temporosphenoidal abscess resulted, and in the third there was a tuberculous tumour in the cerebellar peduncle. Each of these cases was accompanied by tuberculous meningitis, and it is very probable that the meningitis was caused in a similar manner by infection spreading along the perivascular lymphatics.

Fifty-five per cent. of the cases of tuberculous meningitis occurred between the ages of 1 and 5, and it is known that tuberculous otitis media is especially common in children. It is possible, therefore, that the preference of tubercle for the base of the brain may be explained, in some cases, by the fact that infection has taken place through the ear.

Another possible, though perhaps rarer, channel of tuberculous infection is through the labyrinth, for tuberculous disease of the middle ear is frequently associated with destruction of the outer wall of the labyrinth, especially the promontory. In one case the whole of the middle and inner ear was destroyed.

Hertzog (Munich) examined after death the ears of 100 males who were the subjects of pulmonary tuberculosis, and found that seventeen had chronic suppurative otitis media (twenty-one ears in all). Five per cent. of these had labyrinthine suppuration. Kümmel (Hamburg) also considers that labyrinthine suppuration is especially frequent in tuberculous otitis media, for in twenty-six cases operated on by him tuberculous disease of the internal ear was present in six cases. [4].

The evidence that I have been able to collect is not sufficient for any definite conclusion to be drawn, but the frequency with which tuberculous meningitis is associated with infective otitis media suggests the possibility that tuberculous otitis may be a more frequent source of meningeal infection than it was formerly thought to be. It is also possible that general tuberculosis, in some cases, may have its infective source in the middle ear. In the great majority of cases, however, it is probable that the meningitis arises from an independent focus, such as a breaking-down caseous lymphatic gland. In order to properly investigate this subject it is necessary that histological examination of the petrous bone should be made in a large number of cases of tuberculous meningitis.

CHAPTER IV.—LEPTOMENINGITIS.

Ninety-eight cases of infective leptomeningitis associated with infective disease of the ear, excluding those of a tuberculous nature, have been collected. The paths of infection are indicated in the following table:—

I. *Secondary to—*	
(*a*) Cerebral abscess	9 cases
(*b*) Disease of lateral sinus	11 ,,
(*c*) Extradural abscess	12 ,,
(*d*) Cerebellar abscess	2 ,,
II. *Due to direct spread of the disease from—*	
(*a*) Tegmen tympani, mastoid cells or antrum	6 ,,
(*b*) Labyrinth	12 ,,
III. Secondary to pneumonia	6 ,,
IV. Due to exploratory puncture of brain	1 ,,

In thirty-nine cases the path of infection was uncertain.

The situations in which the meningitis was present were:—

Base of the brain	54 cases	Basal only ..	40 cases
		Cerebrospinal	14 ,,
Generalized	36 ,,		
Lateral hemisphere alone	5 ,,		
Ventricle	2 ,,		
Frontal	1 ,,		

§ 1.—*Leptomeningitis Secondary to Cerebral Abscess.*

One of these cases was due to an abscess in the frontal lobe, the remainder were secondary to temporosphenoidal abscess. The meningitis was confined to the base of the brain in six cases, to the left cerebral hemisphere and basal region in two cases, and was generalized in one case. The inflammation was non-purulent in two instances.

Causation.—If the abscess is separated from the surface of the brain by a small portion of grey matter, the pia mater may be infected by direct contact. Should the abscess be situated at a deeper level it may cause meningitis in the following way: The blood-vessels of the pia mater dip down into the white matter, which is often softened and infected in the neighbourhood of the abscess, especially if the latter is of the acute variety, or has become secondarily infected; an infective endophlebitis results and pathogenic organisms are conveyed by the blood-vessels to the pia mater, giving rise to a localized or diffuse meningitis, according as to whether the pathological process is limited by adhesions or not. Finally, the abscess may burst into the intradural space and set up a meningitis which is apt to be very acute and rapidly fatal.

§ 2.—*Leptomeningitis Secondary to Lateral Sinus Thrombosis.*

In six out of the eleven cases of meningitis secondary to this lesion the thrombus was septic, and in three of these cases it was purulent. In the other five cases no mention was made of the nature of the clot. The inflammation of the meninges was limited to the base of the brain in six of the cases, and to the left lateral hemisphere in one case, while in four cases the distribution was general.

Lateral sinus thrombosis can set up a leptomeningitis in the following ways:—

(*a*) By direct contact.

(*b*) By extension of the septic process along one or more of its venous tributaries, i.e., the inferior cerebral and cerebellar veins.

(*c*) By perforation of the inner wall of the sinus taking place with escape of the contents into the intradural space.

§ 3.—*Leptomeningitis Secondary to Extradural Abscess.*

Of the twelve cases in which leptomeningitis was secondary to extradural abscess, seven were due to perisinus abscess, three to suprategminal abscess, while one case resulted from an abscess at the apex of the petrous bone and one from an empyema of the saccus endolymphaticus. With regard to the latter case, it should be mentioned that as no histological examination of the petrous bone was made, this case has been included under this heading and not among those cases secondary to infective labyrinthitis. Passow (Berlin) reports a case in which macroscopically a typical empyema of the saccus endolymphaticus was made out; microscopically, however, the aqueductus vestibuli and saccus were found to be unaffected and that an extradural abscess had simulated an empyema of the sac. Without a histological examination of the petrous bone, therefore, it is impossible to say whether an empyema was present in this case or not.

The meningitis was basal in ten cases, and confined to the right or left lateral hemisphere of the brain in the other two cases.

Causation.—The dura was perforated in seven cases and the pus had escaped into the intradural space, thus infecting the leptomeninges. In the remaining cases infection of the pia-arachnoid was brought about by direct contact, or possibly through venous infection.

§ 4.—*Leptomeningitis Secondary to Cerebellar Abscess.*

Of the two cases of meningitis secondary to an abscess of the cerebellum, the first was non-purulent, the pia-arachnoid covering the abscess being thickened and opaque; in the second the surface of the arachnoid over the upper and outer surface of the cerebellum was coated with yellow lymph. The pia-arachnoid was probably infected by direct extension from the abscess, since the latter in both cases was very near the surface of the brain and separated from the pia mater by only a very thin layer of brain substance.

§ 5.—*By Direct Extension from the Tegmen Tympani, Mastoid Cells or Antrum.*

In six cases the pia-arachnoid may have been infected by direct extension of the disease from the middle ear or its accessory cavities. In four of the cases the bone was carious, and it is possible that the organisms concerned may have directly infected the dura, which in turn infected the vessels of the pia-arachnoid. It seems more probable, however, that the meningitis was caused by an infective thrombosis of a vessel of the tympanic mucosa, continuous with a meningeal vein. This also was probably the path of infection in the two cases which were unassociated with bone disease.

§ 6.—*Infection of the Leptomeninges from the Labyrinth.*

Infective disease of the labyrinth is one of the most important causes of meningitis of otitic origin. Heine [3] reports that fatal otitic meningitis was caused by the labyrinth in 42 per cent. of his cases, while the percentage in Whitehead's series of cases was 27.

Although infective labyrinthitis only gave rise to meningeal infection in twelve of the present series of cases, or 12.2 per cent., it is probable that this percentage is too low, since histological examinations of the petrous bone were only made in the later cases, and without microscopical evidence we cannot exclude the possibility of the labyrinth being the path of infection. In several of the thirty-nine cases, in which the path of infection was uncertain, it is extremely probable that the labyrinth was responsible for the meningitis.

In this section the pathology of labyrinthitis will first be considered, secondly the channels of infection from the middle to the internal ear, and thirdly the paths along which pathogenic micro-organisms are enabled to travel from the labyrinth to the meninges.

Pathology of infective labyrinthitis.—Infective labyrinthitis may be either of the acute or chronic variety. In the acute form the disease is usually diffuse, but is sometimes localized to one portion of the labyrinth. Macroscopically the membranous labyrinth is injected and inflamed, and instead of presenting its normal whitish appearance is bright red in colour. Its cavities may be filled with blood-stained fluid, which later may become purulent; or there may be pus in one chamber and hæmorrhagic effusion in another. Thus in one of the cases [10] the vestibule contained purulent fluid, from which a pure culture of streptococci was grown. The semicircular canals contained hæmorrhagic effusion, while the cochlea contained purulent fluid in its lower coils and blood-stained fluid near its apex. The bony labyrinth soon becomes involved in the inflammatory process, and necrosis of a variable extent of the capsule is very liable to occur. In one of the cases there was very extensive necrosis of the osseous labyrinth, and it is not uncommon to find sequestra in its outer wall during the course of the radical mastoid operation. Tuberculous disease of the middle ear, as before mentioned, is apt to lead to early and extensive destruction of bone; the disease does not always extend to the labyrinth, but a mixed infection is apt to invade the latter through an opening made by the tuberculous process. Extension to the brain or meninges is more liable to occur in the acute than in the chronic form owing to the more rapid progress of the disease in the former, and also to the fact that granulation tissue formation, which tends to limit the extent of the infective process, is not so marked.

The chronic form may be chronic from the commencement, or it may follow the acute variety. It also may be localized or diffuse. It is usually accompanied by extensive formation of granulation tissue, and on opening the labyrinth the presence of suppuration is recognized more by the presence of granulations than of pus. The former may often be observed protruding from fistulæ in the bone or from perforations in the oval or round windows. In one case the canalicular labyrinth was filled with granulation tissue, while in two others the whole of the internal ear was in a condition of chronic granulating labyrinthitis. One case of tuberculous labyrinthitis occurred in which the internal ear was filled with pale granulations which also protruded through the foramen ovale. The bone is often the seat of extensive necrosis, and sequestration of one of the chambers alone, or even of the whole of the internal ear, is sometimes met with. Cholesteatoma is commonly associated with chronic disease of the labyrinth, and it appears to be specially frequent in connexion with fistulæ of the external semicircular canal.

In the acute form the labyrinth may be packed with masses of round-cell infiltration in which the presence of micro-organisms may sometimes be demonstrated. Micro-organisms also may occasionally be found in the substance of an intact fenestral membrane. The inflammatory exudation, though usually diffuse, may be limited to one part of the labyrinth; thus, in one case, the first half-turn of the cochlea was alone affected.

In a typical case of acute diffuse labyrinthitis the scala vestibuli and scala tympani were filled with masses of round cells which were also found in the lacunar spaces of the modiolus. In those cases in which the auditory nerve is involved, if a section of the petrous bone be cut so as to pass through the cribriform plate of the fundus of the internal auditory meatus, the spiral ganglia and nerve-fibres may be found to be infiltrated with round cells. The blood-vessels in the affected portion of the labyrinth are dilated and engorged.

The pathways of infection from middle to internal ear.—The labyrinth may become infected as the result of a traumatic perforation of the capsule, but more commonly as a result of infective middle-ear disease. The former class of case may be due to a fracture of the base of the skull involving the petrous bone. During the past fourteen years ten cases of this form of fracture, leading to meningitis, occurred, but

I cannot find any mention in the notes as to whether the labyrinth was infected or not. Infective labyrinthitis occasionally results from unskilful attempts to remove foreign bodies from the ear, or during the course of a radical mastoid operation from perforation of the capsule, either intentionally or otherwise, by some instrument. Again, a dislocation of the footplate of the stapes during the operation of curetting the tympanic cavity has been responsible for infection of the labyrinth in a few cases. Many more cases, however, are secondary to infective disease of the middle ear.

Labyrinthitis secondary to infective otitis media.—West and Scott, in a paper on the "Operative Surgery of the Labyrinth" [16], published the results of an investigation into the pathways of infection from the middle to the internal ear. They collected a series of cases—twenty-six in all—which had been under their observation in the Aural Department of St. Bartholomew's Hospital, in which the point of infection had been noted during the course of the radical mastoid operation. Their results are as follows:—

Fistulæ of external semicircular canal	11 cases
,, fenestra ovalis	5 ,,
,, promontory	5 ,,
,, fenestra rotunda	1 ,,
,, external canal and fenestra ovalis	1 ,,
Site unknown	3 ,,

Of the twenty-six cases, eleven were associated with cholesteatoma and in six of these there was a fistula of the external canal only, in one a fistulous canal accompanied destruction of the footplate of the stapes, and in two there was isolated destruction of the footplate of the stapes. I have collected thirty-six cases from the same source, which occurred subsequently to these cases, and thus a series of sixty-two consecutive cases is obtained. In all of them labyrinthitis, either localized or diffuse, was present. In my thirty-six cases the paths of infection were as follows:—

Fistula of external semicircular canal	19 cases
,, fenestra ovalis	4 ,,
,, external canal and fenestra ovalis	5 ,,
,, promontory	2 ,,
,, fenestra rotunda	4 ,,
,, foramen ovale and rotundum	1 ,,
,, superior and external canals	1 ,,

Cholesteatoma was present in eleven cases, and in eight of them it was associated with a fistula of the external semicircular canal alone, while in three a fistulous canal accompanied a fistula of the oval window. Taking both series of cases together, we obtain the following result:—

Fistula of external semicircular canal	30 cases
,, fenestra ovalis	9 ,,
,, promontory	7 ,,
,, external canal and fenestra ovalis	6 ,,
,, fenestra rotunda	5 ,,
,, superior and external canals	1 ,,
,, foramen ovale and rotundum	1 ,,
Site unknown	3 ,,

Cholesteatoma was present in twenty-two cases, in eighteen of which fistula of the external canal was present.

Hinsberg [5], in a paper on this subject, collected a comparatively large number of cases, namely 198, but the point of entrance of the infection could only be discovered in sixty-one cases. His results were very similar, they were as follows:—

Fistula of external semicircular canal	27 cases
,, fenestra ovalis	17 ,,
,, promontory	7 ,,
,, in other canals	5 ,,
,, of fenestra ovalis and rotunda	3 ,,
,, fenestra rotunda	3 ,,

Brieger [1] considers that lesions of the fenestral membrane transmit infection to the labyrinth more frequently than fistulæ of the semicircular canals. He states that in four cases of labyrinthine suppuration out of five, infection entered through the foramen rotundum.

It is not, however, essential that there should be an actual fistula in the outer wall of the labyrinth for the latter to become infected from the middle ear. Scott has published a case [11] in which no path of infection was evident to the naked eye. As symptoms pointing to labyrinthitis were present, an operation was performed to examine the outer wall of the labyrinth. No path of infection in the latter could be discovered, the stapes was in position and the promontory of the cochlea and eminence of the external semicircular canal were not fistulous or eroded. The mucosa in the fossula rotunda and in the sinus tympanicus was greatly swollen. The patient died two days later, and at the *post-mortem* examination localized meningitis was found around the pons and medulla, with excess of cerebrospinal fluid in the lateral ventricles of the brain. There was no other evidence of any path of infection in the base of the skull. Sections of the petrous bone were afterwards cut and the labyrinth was found to be in a state of diffuse round-celled infiltration and to contain masses of polymorphonuclear cells and longchained streptococci. Serial sections through the fossula rotunda showed cocci among the cells in the mucosa, in the fenestral membrane, and in the cochlea. The membrane was partly ulcerated, but there was no actual perforation. In this case, therefore, the internal ear became infected through the fenestra rotunda, without any actual opening through its outer wall being present.

Extension of infection from the labyrinth to the meninges.—All the pathways from the labyrinth lead into the posterior cranial fossa, with one exception, namely, a perforation in the anterior crus of the superior vertical canal, in which case the middle fossa may be infected. If infection extends beyond the dura into the intradural space, circumscribed or diffuse meningitis or cerebellar abscess will result. Infection may rapidly spread to the meninges, especially if the lesion be an acute one, or more slowly if it is of a more chronic nature.

Although the course of tuberculous disease of the middle ear is slow, yet, if secondary infection by some pyogenic organism occurs, an acute and rapidly fatal meningitis may result.

Extension of the labyrinthine disease usually follows normal openings in the bone for the auditory nerve and aqueducts of the vestibule and cochlea, infection through the internal auditory meatus being most common. In five of the twelve cases infection spread along the eighth nerve; in the remaining cases, although no note was made as to the condition of the nerve, there was no other obvious lesion. The nerve may be greatly inflamed, and in one case microscopical examination revealed round-celled infiltration of the nerve as it entered the internal auditory meatus. There may be plastic adhesions of lymph around the eighth nerve, or the arachnoid sheaths of the seventh and eighth nerves may be distended with turbid fluid or even pus. The internal auditory canal may contain lymph, thick yellow fluid or pus. The pia-arachnoid in the neighbourhood of the internal auditory meatus may be thickened and adherent to the dura. The arachnoid tissue may be distended with turbid fluid and pus, and in one case there was a cystic collection of fluid around the intracranial portion of the seventh and eighth nerves.

Extension through the aqueductus vestibuli will give rise to an empyema of the saccus endolymphaticus, and infection may spread to the meninges from the latter. An empyema of this sac is not a common sequel to labyrinth infection, since the aqueduct is an extremely minute canal and its lumen is liable to become obliterated by the formation of granulation tissue. Moreover, the arachnoid sheath of the seventh and eighth nerves offers a much easier route for the spread of infection.

One case of an empyema of the saccus endolymphaticus of a doubtful nature has been included among the cases of extradural abscess, since, as previously mentioned, it is impossible to distinguish between an empyema of the sac and a post-tympanic extradural abscess without a histological examination of the labyrinth, and this examination, unfortunately, was not carried out in this instance.

Extension through the aqueductus cochleæ may possibly cause lateral sinus thrombosis, for the aqueduct transmits a small vein which drains into the lateral sinus. Infection of the meninges may possibly occur by this channel, but if so it appears to be extremely rare.

Labyrinthine suppuration may open up new pathways of infection through the capsule. Thus erosion of the superior canals might give rise to an extradural abscess, or possibly to meningitis by direct extension without the formation of any abscess.

Hinsberg [5] reports 198 cases of labyrinthine infection, the cranial cavity being infected in 108. In 43 the pathway of infection could be traced, viz. :—

Through the internal auditory meatus	25 cases
,, ,, ,, ,, and aqueductus vestibuli ..	1 ,,
,, aqueductus vestibuli	8 ,,
,, ,, cochleæ	1 ,,
,, fistulæ in vertical canals	8 ,,

When considering the subject of meningitis secondary to infective labyrinthitis, it is necessary to bear in mind the fact that the labyrinth can be infected by spread of the disease from the cerebral meninges. In order to demonstrate this it is necessary to examine both petrous bones histologically, and to show that the labyrinths of both sides are affected, or that the middle-ear cavities are not diseased. In one case the bilateral labyrinthitis was secondary to pneumococcal meningitis. In this case there was no obvious middle-ear disease. On the right side the cochlea contained round-celled infiltration and the footplate of the stapes was in position. On the left side the cochlea presented a similar appearance and the footplate of the stapes was also in its normal position. The mucous membrane of the middle ear did not appear to be affected, though in microscopical section it was thicker and more vascular than normal. On both sides round-celled infiltration surrounded the eighth nerve as it entered the internal auditory meatus. In another case a full histological examination of the petrous bone was made. On both sides there was labyrinthitis which was apparently secondary to the meningitis. The tympanum was normal on both sides. In this case the meningitis was tuberculous.

Goerke [2] examined nineteen temporal bones in cases of cerebrospinal meningitis, and found that they were normal in only two cases. In the other seventeen inflammatory changes were present. The path of infection from the meninges was found to be through the aqueduct of the cochlea in three cases, through the aqueduct of the vestibule in one case, and along the auditory nerve sheath in eleven cases. In the other cases the path was doubtful.

Habermann claims that in every case of severe cerebrospinal meningitis, infection and transmission to the labyrinth take place solely through the aqueducts of the cochlea.

Conclusions.—Infective labyrinthitis most often occurs as a result of suppurative disease of the middle ear, and the labyrinth is especially liable to become infected when the otitis media is accompanied by cholesteatomatous formation. The pathways of infection may be divided into three classes:—

(*a*) Fistula of the external semicircular canal, which is by far the most common.

(*b*) Fistulæ in other situations, of which fistulous openings in the oval and round windows and promontory are the most common.

(*c*) Through round windows without any actual perforation of the membranes. This class of case may possibly be more frequent than it has hitherto been considered to be, especially in acute cases.

With regard to the possibility of infection taking place through the aqueductus Fallopii along the seventh nerve to the internal auditory meatus, I have obtained no evidence to prove that this does occur; on the other hand, in several histological sections from Scott's series that I have examined, while the eighth nerve was infiltrated with round-cells, the seventh in its canal was unaffected.

The labyrinth may also be infected from the cranial cavity in cases of meningitis, especially in the cerebrospinal variety, infection spreading along the arachnoid sheaths of the seventh and eighth nerves.

Spread of infection from the labyrinth to the meninges takes place in the great majority of cases along the sheath of the auditory and facial nerves.

It is possible for the septic process to extend to the meninges along the aqueducts, or through fistulæ in the osseous labyrinth, but no cases of this kind occurred and they appear to be extremely uncommon.

The cases of meningitis secondary to pneumonia require no further consideration, since the otitis in all probability was not directly responsible for the meningitis.

With regard to the thirty-nine cases in which the evidence as to the origin of the meningitis was incomplete, it need only be mentioned that, although the labyrinth was most probably the cause of the meningeal infection in several of them, no microscopical examination was made, and therefore the path of infection is uncertain.

Some of the remaining cases were, no doubt, ordinary instances of meningococcal and pneumococcal meningitis, in which the ear-disease was not the direct cause.

Examination of this series shows that cases of otitic meningitis may be divided into two main classes, namely:—

(1) Cases secondary to some gross intracranial lesion, such as extradural abscess, lateral sinus thrombosis and brain abscess, and possibly to perforative disease of bone, and

(2) Cases in which no gross intracranial lesion can be found.

In the first class of case the cause of the meningitis is usually obvious, and the spread of infection takes place from the different intracranial lesions in a variety of ways which have been indicated in the preceding pages. In the second group of cases the path of infection may not be so evident, although in many cases in which the infection has spread from the labyrinth there are indications, such, for example, as patches of lymph round the nerve-sheaths or round the internal auditory meatus, on one side, which point to the source of the meningitis. In this class of case the paths of infection are either vascular or labyrinthine, and of the two the latter is probably the more common.

It is probable that the cause of otitic meningitis unassociated with gross intracranial lesions, is, in the majority of cases, infection from the labyrinth, and that infection spreads from the latter to the meninges by way of the arachnoid sheaths of the auditory and facial nerves.

CHAPTER V.—GENERAL CONCLUSIONS.

In this paper I have endeavoured to indicate the possible pathways of infection in the various intracranial complications secondary to infective otitis media, and to determine those which may be considered of most importance.

Infection through vascular channels appears to be responsible for most cases of lateral sinus thrombosis, while vascular infection is a cause of extradural and brain abscesses in a large number of cases.

Many cases of extradural abscess are due to disease of the petrous bone, especially its posterior surface and tegmen; in those cases where the bone is unaffected, the dura mater becomes infected through a septic endophlebitis of a vein of the tympanic mucosa extending to a vein of the dura. Cerebral and cerebellar abscesses may be due to direct contact of the brain with diseased dura mater; if perforation of the latter takes place, direct extension to the cerebral substance may occur; if no perforation occurs, the disease may spread to the brain by infection of the veins in the dura, with extension from them to the vessels of the pia-arachnoid, and from the latter to the interior of the brain.

Cerebellar abscess is also often secondary to infective labyrinthitis, extension of the disease taking place along the nerve-sheaths, or directly in the region of the posterior semicircular canal.

Leptomeningitis is either (*a*) secondary to a gross intracranial lesion or bone disease, in which case it is due to the rupture of an abscess into the intradural space or to vascular infection from the lateral sinus, abscess, or bone, as the case may be; or (*b*) to labyrinthitis, with infection spreading along the nerve-sheaths, or vascular infection from the middle ear direct.

The results of this investigation show that infection of the labyrinth is responsible for many cases of cerebellar abscess and meningitis of otitic origin. Formerly, disease of the labyrinth, owing to lack of knowledge as to its pathology, did not receive sufficient attention as a cause of intracranial infection. Of recent years, however, our knowledge of the diseases affecting it, and their bearing on the subject of encephalic infection, has increased rapidly.

At the present time, surgeons when operating for disease of the middle ear pay more attention to fistulæ or necrosis of its inner wall as evidence of possible labyrinthine involvement. Moreover, various clinical tests which have been introduced lately, such as the rotation tests and the caloric and galvanic reactions, when taken together, appear to afford a fairly sure means of diagnosing this condition. In this way many cases of labyrinthine infection are discovered which in earlier years would almost certainly have been overlooked.

A considerable number of cases of tuberculous and cerebrospinal meningitis occur in patients with infective ear-disease in which the latter is not the obvious cause of the meningitis, and the question as to whether the ear can be regarded as being the channel of infection in such cases requires to be further investigated.

In conclusion I take this opportunity of thanking Mr. Ernest West and Mr. Sydney Scott for permitting me to refer to patients who have been under their care. I must also express my gratitude to Mr. Scott for so kindly allowing me to examine his microscopical specimens, and also for much kind advice in the preparation of this paper.

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SOME RARER MANIFESTATIONS OF PARASYPHILIS OF THE NERVOUS SYSTEM.

BY A. READ WILSON, M.D.

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INTRODUCTION.

No sooner was the long dispute, extending over something like thirty years, as to whether syphilis is, or is not, the essential etiological factor in tabes dorsalis and general paralysis of the insane finally settled in the affirmative, than a new contention arose with regard to the exact relationship of these two conditions to each other.

In 1906, however, in his Lumleian lectures on Tabes Dorsalis, Ferrier [12] crystallized the views of most neurologists when he expressed the opinion that tabes and general paralysis are "merely different aspects of the same polymorphic disease."

Fournier [13], to whom more than any other we owe the recognition of parasyphilitic nervous disease—who, indeed, introduced the word—gave a very comprehensive list of affections which, in his opinion, were parasyphilitic.

I.—Acquired syphilis.

(1) Acute hystero-neurasthenia of the secondary period.
(2) Various neurasthenic manifestations of a more advanced stage.
(3) Hystero-syphilis.
(4) Tabes dorsalis.
(5) General paralysis of the insane.

(6) A special form of epilepsy.
(7) A special form of muscular atrophy.

II.—Congenital syphilis.

Numerous dystrophies and malformations; cases of arrested or retarded development; cachexias, non-viability, &c.
Certain cases of simple meningitis in children.
Perhaps some cases of true epilepsy.
Certainly every case of juvenile tabes and juvenile general paralysis.

This is not the whole list, but is sufficient to show that as long ago as 1894 Fournier was regarding parasyphilis as a much wider entity than was generally supposed; in other words, that it included many other manifestations of disease besides tabes and general paralysis and the combination of the two known as tabo-paresis.

Both these conditions are primary progressive nerve-tract degenerations. But there are certain other nervous diseases of this type; and I shall endeavour to show that in some instances they are parasyphilitic, for we meet with them in patients giving a positive Wassermann reaction, whether syphilis is admitted or denied, and we find them more or less frequently, but at all events sometimes, combined with the recognized parasyphilitic manifestations, general paralysis and tabes. The diseases with which I shall concern myself are three in number, viz.:—

Primary Optic Atrophy,
Primary Lateral Sclerosis, and
Progressive Muscular Atrophy.

All these diseases are of the same primary character—a degeneration of neuronic groups. Tabes dorsalis is the manifestation of a degeneration of the spinal sensory protoneurons; general paralysis, of the cortical association neurons; primary optic atrophy, of the visual neurons; primary lateral sclerosis, of the upper motor neurons; progressive muscular atrophy, of the lower motor neurons.

In the case of tabes and general paralysis the essential etiological factor is the same, syphilis; the old oft-quoted alternative factors, "alcohol, hard work, exposure," are the same; the average interval between infection with syphilis and the declaration of symptoms is the same; the average age-incidence is the same; the symptoms and termination are analogous; signs of gross syphilitic lesions are infrequent, since both usually follow mild attacks of syphilis; and the two diseases are frequently combined in one individual. Moreover, both may attack the subjects of either acquired or congenital syphilis.

Some cases of primary optic atrophy, primary lateral sclerosis, and progressive muscular atrophy show an extraordinary analogy to the above—extraordinary, that is, if they are to have a different etiology, but natural enough if considered as parasyphilitic manifestations. Many give histories of syphilis, others have signs of syphilis remaining on their bodies, or they give positive Wassermann reactions. Evidences of gross syphilitic lesions, too, are rare, since the primary stages have in most cases been mild. Alcohol, hard work and exposure are again amongst the most commonly accepted etiological factors. The average interval between syphilitic infection and the appearance of symptoms is about the same as in tabes or general paralysis. The average age incidence is the same, though in primary lateral sclerosis the onset is so gradual that the patients do not seek advice at the commencement. All three are frequently found associated with tabes, less often with general paralysis; cases occur where two of them are associated together, or where multiple combinations are exhibited. About 10 per cent. of general paralytics have tabes too (Byrom Bramwell, [4] Mott [30]); some 4 per cent. of general paralytics have primary optic atrophy (Mott [30]); primary optic atrophy is found in from 10 per cent. (Osler [40]) to 20 per cent. (Norris and Oliver [38]) of tabetics; and 20 per cent. of tabetics exhibit some form of muscular atrophy (Dejerine [8]). Further, undoubted examples of juvenile primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy exist.

I have recently seen it suggested that, although the neuronic degeneration in progressive muscular atrophy is essentially similar to that in tabes, it is rather to be laid to the account of a "yet-to-be-discovered toxin" than to that of syphilis. This is somewhat like setting up an altar to an unknown god—a proceeding natural enough for the philosophers of ancient Athens, but to be deprecated in an age of exact science. A man proved to have committed a certain crime must necessarily be suspected when that crime is exactly reproduced, but failure definitely to bring it home to him is no justification for hanging someone else about whom nothing is known. If the lesions found in progressive muscular atrophy were utterly unlike those produced by any agent of disease yet known to us, an "undiscovered toxin" would be as fair and scientific an hypothesis as Halley's, when he deduced the orbit of the comet which bears his name and predicted the date of its return.

Syphilis is known to be the cause of a vast amount of disease; it is even said that it enters into the etiology of one-third of all the disease of the world, and investigations which are being carried out in Australia under the Victorian Government, reported by Dr. J. W. Barrett, of Melbourne, in a paper recently read before the Royal Society of Medicine, tend to confirm this. This disease has been shown to be the essential cause of the two most common primary nerve-tract degenerations, and it is fair, therefore, to suspect it in diseases where the pathological conditions found after death are on all fours with those of degenerations of established syphilitic origin, as is the case with most examples of primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy.

With regard to the sex-incidence of parasyphilis the proportions given by different compilers of statistics vary between three to one and twenty to one in favour of males. No doubt truth lies between. At all events more men are smitten with parasyphilis of the nervous system than women. Why this should be so is an interesting study. Beyond question more men acquire syphilis than women. A young man contracting the disease from a prostitute, as is often the case, is naturally unable to infect so large a circle as she has the opportunity of doing. When he does pass the infection on the recipient is very probably a member of the same class as the first, and becomes another centre of dissemination for the male sex. So we can only expect to find the disease commoner in men than women. Does this account for the whole discrepancy between the sexes with regard to parasyphilis? Probably not. In the first place, a large proportion of prostitutes never reach the parasyphilitic age. Secondly, very many women who marry syphilized men are protected by Colles' law. The explanation which is often advanced that women are not so liable to contributory causes is not, I think, a sound one: partly because I do not believe contributory causes play a sufficiently large part in the etiology, and partly because the great majority of women are exposed to stress or strain just as frequently as men, though such stress may take a different form.

The sex-incidence in congenital parasyphilis is of course equal. Still [50] finds that in the cerebral palsies of children the number of boys attacked is to the number of girls as three is to two.

	Boys	Girls
Infantile hemiplegia	32	19
Spastic paraplegia	14	12
,, diplegia	14	8
,, monoplegia	1	0

It will be seen that in spastic paraplegia the sex-incidence is almost the same; and this may be significant with regard to congenital syphilis.

I shall not attempt to prove that every example of primary optic atrophy, primary lateral sclerosis, and progressive muscular atrophy is parasyphilitic. Primary optic atrophy undoubtedly occurs as a sequela or complication in lead poisoning, some specific fevers, diabetes; yet it is not an invariable complication, and investigation may conceivably show that it is only manifested in persons who have a congenital or acquired syphilitic taint. Also, up to the present, so few cases, comparatively, of primary lateral sclerosis or progressive muscular atrophy have been proved to be parasyphilitic. Even in tabes, where the percentage of unquestionable parasyphilis is so high as 90, the other 10 per cent. are not proven; and, until they are, one cannot deem unreasonable those who suppose that some other agent may possibly, though very rarely, cause progressive bilateral degeneration in the posterior columns of the cord. For if one poison—to wit, the virus of syphilis—can produce the disease, why should not another under favourable conditions occasionally do the same?

I do not therefore attempt to gather every case of primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy into the parasyphilitic net. But the analogies to tabes and general paralysis, together with the fact of their frequent occurrence in combination with these diseases, constitute strong evidence that at all events some cases are parasyphilitic in character. From time to time articles appear in the literature in which the connection of syphilis with these three diseases is recognized and brought out. Thus Mott [31] brackets together general paralysis of the insane, tabes and primary optic atrophy, and describes them as "really a single morbid entity, owning one cause, with an insidious onset, progressive in character, and uninfluenced by anti-syphilitic remedies—in fact, a primary neuronic dystrophy. They may occur successively or simultaneously in the same individual." And again, "It is probable that Erb's spinal paralysis and certain cases of amyotrophic lateral sclerosis may be primary post-syphilitic dystrophies."

The recognition of progressive muscular atrophy as a parasyphilitic manifestation is much further advanced on the Continent, particularly in France, than in England. Fournier [13] placed a "special form of muscular atrophy" in his classification of parasyphilitic affections. Other observers who have published cases to show the parasyphilitic nature of progressive muscular atrophy are Poussard [43], Leri [25], Camus [5], Lannois et Poret [24], van Gehuchten [15], Merle [27], Kinnier Wilson [53], Rose et Rendu [46]. The last-named authors point out that amyotrophies in tabes, due to peripheral neuritis, affect the lower limbs, whereas those of central origin have a preference for the upper extremities, though the legs are not exempt. In the arms the type is usually that of Aran and Duchenne, or else the shoulder-girdle is most affected. As a rule the degeneration is symmetrical, though one side may be more advanced than the other. Raymond [45] recorded the case of a man who, eleven years after syphilitic infection, suffered from lightning pains in the right shoulder, and four years later developed a progressive atrophy in the muscles of the right hand, spreading to the arm and shoulder. In the following year the left arm was similarly attacked. The muscles at the back of the neck were atrophied equally.

Most of my material has been collected in the various departments of Guy's Hospital, and the laboratory tests have been carried out by the bacteriological department according to Wassermann's original method, except that the rabbits are immunized against human instead of sheep's corpuscles. But I am also indebted to Dr. T. E. K. Stansfield for permission to investigate patients with general paralysis in the London County Asylum at Bexley. In those cases the cytological examination of cerebrospinal fluids, together with the butyric acid, ammonium sulphate and sodium glycocholate precipitation tests, were carried out by Dr. George Evans; whilst the Wassermann tests were all undertaken at Claybury by Dr. J. P. Candler, who also follows the original method, except in the source of the corpuscles, ox blood being used instead of sheep's.

CHAPTER I.—THE CEREBROSPINAL FLUID AND THE WASSERMANN REACTION.

It is unnecessary here to enter into the details of the composition of cerebrospinal fluid, or of the technique of the Wassermann reaction, either in its original form or the modifications introduced by Hecht or Fleming. Neither is it requisite to trace the steps by which the original explanation of the reaction was shattered, nor to enter the discussion as to whether the reaction is, or is not, infallible. All I will say is that the test is probably specific for syphilis and parasyphilis (for though certain cases of malaria give it, malaria is not clinically liable to be confounded with syphilitic disease); yet it does not indicate the organ affected.

If the central nervous system is not affected the reaction will usually be positive with the serum, and negative with the cerebrospinal fluid. This is natural when we remember that the latter is essentially a secretion. But even in general paralysis the cerebrospinal fluid is very occasionally negative, whilst the serum is positive. Plaut [42] tested both fluids in ninety-five cases of general paralysis, and got a positive reaction with the serum in every case, and in all but one with the cerebrospinal fluid.

In syphilis and parasyphilis there is marked lymphocytosis of the cerebrospinal fluid. This ebbs or flows along with the activity of the disease, and is therefore useful as an index not only to that activity or quiescence, but to the effect of antisyphilitic remedies, whose exhibition in parasyphilis produces no good effect on the disease, and no effect on cerebrospinal lymphocytosis; but in syphilitic meningitis, for instance, as the patient recovers so the lymphocytosis decreases. This lymphocytosis occurs in some other diseases, e.g., sleeping-sickness and herpes zoster, and so cannot be considered absolutely pathognomonic; but its presence is a valuable sign when combined with other facts.

CHAPTER II.—FORMS ASSUMED BY PARASYPHILIS OF THE NERVOUS SYSTEM.

A vast amount of evidence had to be presented by Fournier [14], Gowers [16], Erb [10], in particular, and others before the medical profession accepted the dicta "no syphilis, no tabes," and "no syphilis, no general paralysis of the insane." No such voluminous evidence is forthcoming with regard to primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy. These are very much rarer manifestations, and, not being considered parasyphilitic, more attention has been paid etiologically to alcohol, exposure, and particularly to hard work than to syphilis. Many reports do not mention syphilis at all, or pass it over lightly with "No history of syphilis was given," and very few cases as yet have been subjected to the Wassermann test. When, however, there are signs of tabes or general paralysis in conjunction, syphilis is inquired after carefully and the blood is tested.

Before tabes or general paralysis were recognized as parasyphilitic, the percentage of cases giving a history of syphilis was quite low; but when Fournier, Gowers and Erb were insisting on its etiological importance the figures of competent observers jumped up in a surprising manner. For instance, Bernhardt's [3] rose from 21 per cent. to 60 per cent.; Oppenheim's [39] from 17 per cent. to 80 per cent.; and Rumpf's [47] from 65 per cent. to 80 per cent. The same thing occurred with general paralysis; and it might well be true of the others, were more care taken in the investigation of histories. Not long ago a case of suspected amyotrophic tabes was brought before the Neurological Section of a certain learned society. The patient was 36 years old and gave a positive Wassermann reaction. She had obvious tabes, and in addition wasting of the small muscles of the hands, particularly the left hand. The patient was a charwoman, and the Section came to the conclusion that the muscular atrophy was due to her occupation, explaining the more advanced condition of the left hand as due—upon what grounds I know not—to greater pressure upon that hand in the process of scrubbing floors.

If one group of neurons can degenerate as a result of antecedent syphilis, why not another group, or any other? If both tract degenerations can be explained as parasyphilitic in tabo-paresis, why not in tabes combined with progressive muscular atrophy? Yet we find constantly this seeking for a separate and distinct cause in cases where either tabes or general paralysis are combined with some other tract degeneration.

Of all the conditions of degeneration which, rightly or wrongly, have been laid to the account of syphilis by different writers, I propose to confine myself to pure instances of primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy, and combinations of these, either with each other or with tabes or with general paralysis. If any of the other suggested parasyphilitic manifestations are mentioned they will only be referred to incidentally, except in the case of tabo-paresis, which I shall take as the prototype of the coincidence in one individual of two separate parasyphilitic tract degenerations.

My subject can therefore be divided into the following two sections with fourteen subsections:—

(I) *Uncomplicated.*
  (*a*) Primary optic atrophy.
  (*b*) Primary lateral sclerosis.
  (*c*) Progressive muscular atrophy.

(II) *Complicated.*
  (*d*) Tabes combined with general paralysis.
  (*e*) Tabes combined with primary optic atrophy.
  (*f*) Tabes combined with primary lateral sclerosis.
  (*g*) Tabes combined with progressive muscular atrophy.
  (*h*) General paralysis combined with primary optic atrophy.
  (*i*) General paralysis combined with primary lateral sclerosis.

(*j*) General paralysis combined with progressive muscular atrophy.

(*k*) Primary optic atrophy combined with primary lateral sclerosis.

(*l*) Primary optic atrophy combined with progressive muscular atrophy.

(*m*) Primary lateral sclerosis combined with progressive muscular atrophy.

(*n*) Cases where more than two of the symptom-groups are manifested in one individual.

Some of these are comparatively common affections, others are rare, and although I cannot cite an actual case of primary optic atrophy combined with progressive muscular atrophy, there is no theoretical reason why it should not exist.

In each of these there is a definite degeneration in brain or cord, or nerve-trunk, which can be anticipated from a knowledge of the symptoms, and can be demonstrated *post-mortem*.

In (*a*) there will be degeneration of the optic nerve alone.

In (*b*) there will be degeneration of the upper motor neurons.

In (*c*) there will be degeneration of the lower motor neurons.

In (*d*) there will be degeneration of the spinal sensory neurons and of the cortical association neurons.

In (*e*) there will be degeneration of the spinal sensory neurons and of the optic nerve neurons.

In (*f*) there will be degeneration of the spinal sensory neurons and the upper motor neurons.

In (*g*) there will be degeneration of the spinal sensory neurons and of the lower motor neurons.

In (*h*) there will be degeneration of the cortical neurons and of the optic nerve neurons.

In (*i*) there will be degeneration of the cortical neurons and of the upper motor neurons.

In (*j*) there will be degeneration of the cortical neurons and of the lower motor neurons.

In (*k*) there will be degeneration of the optic nerve and of the upper motor neurons.

In (*l*) there will be degeneration of the optic nerve and of the lower motor neurons.

In (*m*) there will be degeneration of both the upper and lower motor neurons.

In (*n*) there may be degenerations of any combination of these tracts.

The decay of the affected tract may be rapid, as in primary optic atrophy or general paralysis of the insane; or slow, as in tabes, primary lateral sclerosis or progressive muscular atrophy.

Norris and Oliver [38] give the average length of time for primary optic atrophy to progress to total blindness as about one year—it varies from a few months up to fifteen years. General paralysis usually ends fatally in from two to three years. The other three conditions may drag on very much longer.

It has been remarked that when two parasyphilitic manifestations are present in one individual, there is a tendency for the disease to progress more slowly. Benedikt [2], as long ago as 1881, pointed out that primary optic atrophy coming on in the pre-ataxic stage of tabes exercised a favourable influence, and retarded the symptoms. If this amelioration of the symptoms of one tract degeneration produced by the coincidence of a second is a reality, it might tend to show that both the degenerations were due to one cause. For if two totally distinct causes were at work there could be no reason why one should be favourably affected by the other, whereas if one virus were, so to speak, dividing its attention between two or more tracts it might be argued that it would have less energy to devote to either one of them, and so each would be retarded.

Some, if not all, of these conditions may be simulated by active syphilis; for example, a man may have the signs and symptoms of spastic paraplegia with a history of syphilis and a positive Wassermann, and yet under the influence of antisyphilitic remedies the condition clears up; thus proving that the condition was syphilitic (*i.e.*, gummatous, or due to syphilitic meningitis) and not parasyphilitic. Parasyphilis is unaffected by the antisyphilitic remedies, namely, mercury and potassium iodide; but whether it will be found that it is amenable to salvarsan injections the evidence at our disposal is at present insufficient to determine. Amongst the cases recorded later there is one (Case 19) entirely unaffected by mercury and potassium iodide, which, after salvarsan injection, gave a negative Wassermann, though the reaction was positive before. The interval, however, in this case between the injection and the change in the Wassermann reaction was so short—only two weeks—that perhaps it is of no importance. It might by itself be looked upon as a hopeful indication, seeing that it has been considered a rule that, although parasyphilis may not at first give a positive Wassermann, when in the progress of the case the reaction has once become positive the patient does not afterwards give a negative one.

A general distinction between a true and false parasyphilitic manifestation may be drawn thus:—

Parasyphilis.	*Pseudo-parasyphilis.*
(1) First symptoms not generally noticed till eight to fifteen years or longer after primary infection.	(1) First symptoms noticed less than eight years, and often very soon, after primary infection.
(2) Average age-incidence 37 years.	(2) Very many patients are under 25 years of age.
(3) Begins usually after all syphilitic manifestations have disappeared.	(3) Tertiary or late secondary manifestations may co-exist.
(4) Onset insidious as a rule and progress not very rapid.	(4) Onset often sudden, often determined by an accident, as a fall or a blow, and progress rapid.
(5) History of syphilis as a rule shows few and mild early symptoms.	(5) History of syphilis often shows a severe attack.
(6) Reaction to antisyphilitic remedies *nil*, or injurious.	(6) Reaction to antisyphilitic drugs marked and beneficial.

Head [19] suggests that in spinal cases where the onset is sudden the prognosis is bad. But in parasyphilis the prognosis is bad whether the onset be sudden or slow. In syphilitic disease of the cord the prognosis depends more upon the lesion than upon the suddenness or otherwise of the attack. In thrombosis and hæmorrhage the onset is likely to be most sudden, and certainly in such the prognosis is grave, for it is difficult to see how antisyphilitic or any other remedies are going to remove thrombus or clot, at all events in time to prevent permanent damage to the nervous elements from softening or compression. But in cases where the symptoms are due to gumma, or thickening of meninges, recovery is by no means rare under antisyphilitic treatment.

Wassermann's test is of great value in the differential diagnosis of parasyphilis and pseudo-parasyphilis, as the following three cases mentioned by Mott [29] indicate.

(1) A woman was admitted to an asylum as a general paralytic; she exhibited cerebrospinal lymphocytosis, but the Wassermann reaction was negative. Under treatment by mercurial inunction the symptoms of general paralysis cleared up.

(2) A man was admitted to an asylum as a general paralytic. He improved so greatly that he would have been discharged as cured but for the fact that his cerebrospinal fluid gave a positive Wassermann

reaction. Suddenly he began to have seizures and died. *Post-mortem* his brain showed lesions of general paralysis of the insane.

(3) A woman with definite tabetic symptoms, but who had probably been infected less than four years before, showed intense cerebrospinal lymphocytosis, but a negative Wassermann reaction. The symptoms cleared up under mercurial inunction. This case shows the value of giving anti-syphilitic treatment a trial in apparent parasyphilis of the nervous system when the Wassermann reaction is negative.

It is commonly said, and observation tends to confirm the view, that parasyphilitic nervous disease as a rule follows an apparently mild attack of syphilis. If, however, we consider the terminal nervous degeneration as really an ultimate part of the attack, it cannot in its totality be described as mild. Mott [32] quotes Fournier as saying that: "If the virus expends itself in severe primary or secondary manifestations there is less tendency to parasyphilis afterwards," and Mott, himself, was surprised at the rarity of tertiary lesions in over 500 *post-mortem* examinations on general paralytics. He says, further, that in spite of the well-known debauchery and sexual promiscuity of many general paralytics in the early stage of the disease, he has never seen a primary sore or secondary rash on such a patient. Krafft-Ebing [23] confirms this observation, and put it, as well as the "no syphilis—no general paralysis" dictum, to a severe test; he selected nine patients suffering from general paralysis of the insane who gave no history of syphilis and who had no physical signs of the disease about their bodies, and inoculated them by injecting the virus from a typical hard chancre; none of them developed syphilis, showing that they had become insusceptible to the disease.

Syphilis established in a race tends to produce racial syphilization with consequent inherited insusceptibility, and, as a result, we see fewer cases of severe syphilis than in former generations. Yet there are more cases of tabes and general paralysis. May this not be because the population increases, and consequently there are more cases of syphilis than formerly, although of a milder character, parasyphilitic degenerations being more apt to follow mild attacks in which the virus has not spent itself riotously in the early stages?

Why do the effects of syphilitic inoculation differ so widely? Why should the disease in one patient, with apparently a mild attack, lead, after a period of entire quiescence, to such grave and devastating degenerations of the nervous system, while another, with what appears a far more severe infection, develops no nervous symptoms in after life at all? Is the difference in the *Spirochæta pallida* or in the patient's resistance, the defensive reaction excited in the tissues by the presence of the virus? And, if it is a question of resistance, is it the resistance of the organism as a whole or of the individual tissues? Comparison with malaria indicates the possibility of the existence of varieties of the spirochæte. Or the virus may be modified by passage through certain individuals, or the treatment of the disease may modify the virus. This last, however, is hardly likely, seeing that precisely the same ultimate nervous degeneration may overtake a man who never had any treatment with mercury at all as one who underwent a prolonged course; unless we allow that the murcurial modification of the virus occurred during passage through a previous individual. The following remarkable instances, quoted by Mott [33], point strongly in the direction of there being at all events a special neurotoxic variety of the spirochæte, or a special neurotoxic modification of the virus.

Two students were infected with syphilis on the same day by the same woman; both died fifteen years later of general paralysis (Babinski). Two men were infected with syphilis about the same time by the same nurse; both were general paralytics ten years afterwards (Mott). Two men acquired syphilis from the same source about the same time; ten years later both were subjects of tabes dorsalis (Marie and Bernard). Four men were infected with syphilis by one woman, and later all suffered from either tabes or general paralysis; a fifth man who also had connexion with this woman, but did not contract syphilis, did not develop either tabes or general paralysis (Erb). Seven glass-blowers were under treatment together for chancre of the lip. Ten years later five of them came under observation, and four were suffering from tabes or general paralysis (Brosius). This extraordinary example is given by Morell-Lavallée [28]:—

Marthe X., in 1870 the mistress of Primus (medical student); he died in 1873 of syphilitic meningitis.

In 1871 she was the mistress of Secundus (medical student); he married later and had healthy children, but died in 1888 from general paralysis.

In 1872 the mistress of Tertius (medical student); he married later and had two healthy children, but died in 1882 from general paralysis.

Later the mistress of Quartus (chemist); he died in 1890 from general paralysis.

Later the mistress of Quintus (engineer); he died of "folie syphilitique." The whole five being infected with syphilis by this woman.

Yet experiments on animals do not uphold the theory of variation in the spirochæte, or of modification of the virus so as to be specially toxic to given tissues; for there appears to be no difference in the lesions produced by inoculating apes with virus obtained from a wide range of syphilitic lesions. And a chimpanzee inoculated with virus from a syphilized monkey (*Macaque*)—which does not react well to the disease, and might, therefore, be supposed to modify the virus by passage—shows similar and equally severe lesions as one inoculated directly from a human subject. Therefore, until further light is thrown on the question, we must consider that the variations in the symptom-complex are due, not to the virus but to the differences in resistance of the individuals attacked—difficult as it undoubtedly is to explain the above quoted instances simply as coincidences.

Profeta's law, that a non-syphilitic child of a syphilitic mother does not acquire syphilis from the syphilitic mother who suckles it; and Colles' law, that a non-syphilitic mother does not contract syphilis when suckling her syphilitic child, whereas a wet nurse does, show that immunity is attained by the child or mother acquiring some antitoxic substance from the other.

In a large number of cases of congenital general paralysis, Mott [34] obtained a history of frequent miscarriages in the mother and of her bearing typical syphilitic children, without herself acquiring the disease. In two instances the mother died of general paralysis, whilst a considerable number of the fathers succumbed to this disease. The usual conjugal history of the parents of juvenile parasyphilitics is of this type: First a longer or shorter series of miscarriages; then children born dead, and children dying in infancy—often from hydrocephalus or meningitis; then children apparently healthy, but who later show premature nervous decay, suffering for example from nerve deafness, optic atrophy, tabes or general paralysis; and finally healthy children, indicating either that in the course of time the virus becomes attenuated, or that the resistance of the offspring increases in strength, or that both these processes are in operation together. Occasionally, however, a child with signs of inherited syphilis, or a parasyphilitic child, may be born out of its turn as it were, after several healthy ones. Levaditi has actually observed the *Spirochæta pallida* within the ovum, and the phenomenon may be explained by the virus attacking one ovum and not another, or by this particular ovum having less resistance than previously fertilized ones.

How can the degeneration of particular groups of neurons be accounted for? Why should one parasyphilitic individual suffer from tabes, another from general paralysis, others from primary optic atrophy, primary lateral sclerosis or progressive muscular atrophy, or others from combinations of two or more of these together? In direct syphilis of the nervous system the particular position of the lesion is probably fortuitous, there being an accidental metastasis of the organism at that spot. This cannot be the case in parasyphilis, for though a variety of symptoms may be present, yet the very constant occurrence of the Argyll-Robertson pupil—which is probably only met with in parasyphilis of the nervous system—shows that the incidence cannot be random and uncontrolled. Neither spirochætes nor antigens have ever been demonstrated in the cerebrospinal fluid (though inoculation of apes with that fluid is said to have been followed by the development of syphilis); but antibodies are found, or at least the unknown substance which acts the part of antibody in Wassermann's reaction, and probably in direct proportion to the neuronic decay. Nerve-cells are not capable of regeneration, though their processes are; and when decay sets in it begins in the dendrites and travels back finally to the cell and its nucleus. Most infections are short lived and fleeting in effect, and the tissues attacked are not usually so injured as to preclude recovery sooner or later. But syphilitic infection is unfortunately prolonged, at the best severe, and the individual attacked never knows when he is at the end of his troubles; often it lasts till the end of the victim's life, and very frequently either directly or indirectly brings about his death. When such a prolonged evil influence is brought to bear on nervous tissues it leads to permanent and irreparable damage—premature decay and death.

Bacterial infections may be important in determining the locality of parasyphilitic degeneration, by lowering the resistance of one group of neurons more than another, and they may also be the immediate factor in the onset of the disease, or produce aggravation of symptoms and acceleration of decay. Parasyphilitics not only readily fall victims to microbic infections, but are especially liable to be carried off by them, or to show increased rapidity in the progress of the disease as a result of such attack. Possibly the toxic effects of secondary bacterial infections are greatly increased by the presence of the increased quantity of lipoids in the blood, consequent on the nervous decay.

The Argyll-Robertson pupil is the most constant physical sign of parasyphilis of the nervous system and occurs rarely in diseases that are due to syphilis or its sequelæ. Babinski pointed out that the phenomenon of the Argyll-Robertson pupil is not confined to tabes or general paralysis, but may be found in other post-syphilitic states.

It may well be, when in course of time parasyphilitic manifestations come to be more fully recognized and classified, that the Argyll-Robertson pupil will hold the first place as the commonest of them all. Whether it ever occurs as the only sign is difficult to determine —patients do not seek advice for loss of light reflex. It is so commonly found with tabes, general paralysis, and primary optic atrophy, as to be regarded as a symptom of all three ; but in the case of tabes, at all events, it is difficult to see how degeneration of the ciliary ganglion can be in any way the result of degeneration in the posterior columns of the lower cord, and yet the Argyll-Robertson pupil is often found so early in the disease that the only other sign may be an absent tendo-Achillis jerk. It is more easy to understand the ganglion degeneration as a concomitant of the spinal degeneration, owning a common cause with it, than as its result. Similarly, in general paralysis with the phenomenon, both are probably separate manifestations of a primary condition. With primary optic atrophy, if the pupil light reflex were not lost till after blindness had occurred, it might be argued very fairly that it was due to the non-perception of the light stimulus, but it is found before vision is lost. Here again we may have two results of one protean disease.

The motor nerves of the extrinsic ocular muscles are frequently affected in parasyphilis, producing ptosis and various ophthalmoplegias. These may be due to a peripheral neuritic condition; but in some cases where the paralysis does not vary, as it does in the neuritic ones, the disorder may be due to a lower neuron degeneration, a parasyphilitic progressive muscular atrophy in fact. Merely a different aspect of the same polymorphic disease.

If a number of the different groups and systems of neurons of which the central nervous system is made up are liable to degeneration as the result of syphilis—or even all of them—clinical experience yet shows that some of these groups are more prone to be affected than others, have less resistance than others. Individuals vary as to which set is affected first and to the greatest extent, but we shall not be far wrong if we place the groups in the following order, beginning with the least resistant: (1) Ciliary ganglion; (2) spinal sensory protoneurons; (3) cortical association neurons; (4) optic nerve; (5) pyramidal tracts; (6) anterior cornual cells—lower motor neurons.

If organic life could be prolonged sufficiently, independently of the central nervous system, we might expect to find that every case of parasyphilitic nervous disease, in whatever tract it commenced, would progress more or less rapidly, to complete nervous death.

Fournier [13] apparently makes a mistake in his classification of parasyphilitic affections in including the first subdivision, for early neurasthenia after syphilitic infection is amenable to anti-syphilitic remedies, and therefore not parasyphilitic.

"But a neurasthenia occurring in a syphilitic patient in the tertiary stage is very persistent and always results in permanent disturbance of the nervous system" (Fournier). This form is never benefited by antisyphilitic remedies. Such cases are to be considered as early parasyphilis. For though as a rule parasyphilis of the nervous system does not manifest itself until eight to fifteen years after infection, yet cases of an undoubtedly parasyphilitic nature do sometimes show their first symptoms within even two or three years after infection. Parasyphilis, in fact, conforms to no rules. There is, however, I think, evidence to show the existence of a tendency, where syphilis has been acquired early in life, for parasyphilis to appear late; and where the patient is more advanced in age at the time of infection, for the interval until parasyphilis shows itself (the incubation period of parasyphilis we might call it) to be shortened. Erb [11] calls attention to this latter point; but the instances he gives are not of much value, seeing that amongst them the lowest age at which infection occurred was 48. Still in that case the "incubation period" was the longest of the series, which is as follows:—

(1) Syphilis acquired at 48, tabes developed at 58.
(2) Syphilis acquired at 57, tabes developed at 66.
(3) Syphilis acquired at 54, tabes developed at 59.
(4) Syphilis acquired at 48, tabes developed at 54.
(5) Syphilis acquired at 55, tabes developed at 57.
(6) Syphilis acquired at 55, tabes developed at 58.
(7) Syphilis acquired at 68, tabes developed at 70.

The interval of time between infection and the first appearance of symptoms of parasyphilitic nervous disease varies from three to thirty years, though exceptional cases may be found outside these limits, as in the fifth and seventh of the above series, where the interval was only two years; and in Case 9, recorded later, in which the interval was as long as fifty years. But the average is eight to fifteen years; it depends on the intensity of the virus and the efficiency of the resistance. *Ceteris paribus*, one would expect the incubation period to be longer when the disease is acquired young, for the younger the patient the greater will be his resistance, and the longer will he be able to hold out against the enemy. On the other hand, cerebral and spinal syphilis may occur at any period after infection, and a large number suffer before they are 25 years old.

In congenital cases the first manifestation of parasyphilis usually occurs about puberty, but this is by no means constant, for it may develop much earlier, as in Still's cases quoted above [50], and it may well be that some of the cases of parasyphilis developing during the third decade, where acquired syphilis is denied and cannot be demonstrated, are due to hereditary disease. It would even seem possible that some much later cases are of the same type, for Christian Müller [36] has recorded two virgins who developed general paralysis at the end of the fourth decade and died therefrom at the ages of 42 and 43 respectively.

Fournier considers as parasyphilitic all cases of epilepsy in which the first symptom appears after the age of 35 years. Rumpf [48] puts the same proposition less dogmatically, and says that it is rare for epilepsy occurring after the age of 30 and progressing to motor paralysis to be other than parasyphilitic.

Fournier gives the following example: A man, aged 45, who had suffered from a mild attack of syphilis twenty years previously, suddenly developed *grand mal*, which recurred at intervals for many years, with frequent attacks of *petit mal* interspersed. He exhibited no other symptoms. Max Nonne [37] says he has seen several such cases, and relates two where epilepsy preceded locomotor ataxia. (1) A man, aged 45, two and a half years after infection with syphilis developed epileptic attacks occurring three or four times a month. A year later primary optic atrophy appeared and lightning pains, the case progressing to one of tabes. (2) A man, aged 40, four years after infection developed epilepsy. Three years later he developed definite tabes with absent knee-jerks, typical pupils and ataxy. Neither of these cases was affected by mercury or potassium iodide. Head [20] records a case which is probably one of parasyphilitic epilepsy. A man, aged 39, had a chancre thirteen years previously, for which he was treated with mercury for eighteen months. Three years after infection he began to have attacks of minor epilepsy consisting of momentary unconsciousness. Six years later attacks of *grand mal* began. Each attack was preceded by hours or days of intense headache. The jaw went over to the right and unconsciousness followed. There were no abnormal signs in the nervous system; the discs were normal. Further discussion of parasyphilitic epilepsy, interesting though it is, would be outside the scope of this paper, and I will proceed to deal, *seriatim*, with the various subdivisions into which I have previously tabulated my subject. It will, however, be more convenient to take them in a different order.

CHAPTER III.—TABO-PARESIS AS THE PROTOTYPE OF COMBINED PARASYPHILITIC DISEASE OF THE NERVOUS SYSTEM.

If tabes and general paralysis are simply different manifestations of one polymorphic disease—if, in fact, they are really one disease, it is perfectly simple to understand the combination of symptoms which we see in cases of tabo-paresis. Though the variations are so numerous they are governed by the varying intensity of degeneration at different points throughout the affected neuronic systems. When we consider how many different functions may be influenced more or less seriously by degeneration of the posterior columns of the cord, or of the association neurons in the cortex, we see why tabo-paresis does not conform to one type—why, indeed, it is almost impossible to find two cases precisely alike. When the two factors are subject to almost innumerable variations, the results of their union must be more variable still. And so we find general paralytics with absent ankle-jerks, or with ataxic gait, or with perforating ulcers, or lightning pains, or loss of sexual power, or exhibiting Romberg's sign, or with two or three or all of these together, indicating decay of the spinal sensory tracts in addition to cerebral degeneration.

Case 1 is an example of general paralysis of the insane with one sign of tabes.

Alfred G., aged 50, had syphilis when 18. He gives a positive Wassermann reaction as well as the cerebrospinal precipitation tests. He has well-marked mental signs and tremors of general paralysis, his pupils are unequal, irregular and of the Argyll-Robertson type. There is slight ptosis on both sides. His gait is normal but his knee-jerks are absent.

Case 2 is a similar instance in a man who gave no history of syphilis.

George C., aged 38, gives a positive Wassermann reaction both with serum and cerebrospinal fluid; the latter also shows lymphocytosis and gives the precipitation tests. He has the mental symptoms—tremors and slurred speech—of general paralysis. His pupils are unequal, irregular and of the Argyll-Robertson type. His gait is normal but his knee-jerks are absent.

The tabetic signs may be, much more rarely, manifested in the upper extremities and not in the lower. A general paralytic may exhibit Biernacki's sign, that is, loss of sensibility to pressure on the ulnar nerve behind the elbow; or he may be anæsthetic over the distribution of the ulnar nerve; he may have loss of joint sense, not knowing where his limbs are placed without looking; or loss of muscle sense, being unable to distinguish between the weights of different objects of similar size; or he cannot, with his eyes shut, recognize an object placed in his hand; or his arms may be inco-ordinate in their action. On the other hand, we may have a tabetic patient who has, in addition, one or more signs of general paralysis of the insane. Perhaps he has grandiose ideas, or his speech becomes slurred; or he develops tremors of the tongue or lips, or some form of aphasia may appear. Naturally tabo-paretics are as liable to have Argyll-Robertson pupils as patients suffering from general paralysis or tabes uncombined.

Case 3.—Here the spinal symptoms were the more marked.

Henry C., aged 47. He admitted syphilis but could not tell the date. Wassermann reaction is positive and his cerebrospinal fluid shows lymphocytosis and the precipitation tests. His gait is ataxic, he exhibits Romberg's sign, he has a perforating ulcer, and his knee-jerks are absent. His pupils are unequal, irregular and of the Argyll-Robertson type. He further shows distinctly the mental signs of general paralysis of the insane.

Case 4 is similar but without a history of syphilis.

Frederick P., aged 45. Wassermann reaction and cerebrospinal precipitation tests positive. His gait is unsteady, he shows Romberg's sign, and his knee-jerks are absent. His pupils are unequal, irregular and of the Argyll-Robertson type. In addition he has the mental symptoms and slurred speech of general paralysis well marked, but there are no tremors.

Such, then, is the picture when the two commonest manifestations of the one polymorphic disease are combined together.

Of the three conditions—primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy—the first is by far the most common. It is so frequently found in conjunction with tabes, and is so often manifested in congenital syphilitics, that, although some neurologists—notably Mott—recognize it as "merely a different aspect of the same polymorphic disease," it is surprising that it has not long ago been generally accorded a position amongst parasyphilitic manifestations. Yet when it has occurred in combination it has simply been considered as a symptom, and when alone frequently as "optic atrophy of unknown cause."

CHAPTER IV.—PRIMARY OPTIC ATROPHY AS A PARASYPHILITIC MANIFESTATION, EITHER COMBINED OR ALONE.

(*a*) *Primary Optic Atrophy combined with Tabes.*

Just as we saw, in speaking of tabo-paresis, that there is the utmost variety in the cases according to the exact position and extent of the neuronic degeneration, so in primary optic atrophy with tabes we may have every gradation in the intensity of tabes shown, from mere loss of tendo-Achillis jerks to well-marked locomotor ataxia.

Norris and Oliver [38] compute that 20 per cent. of tabetics have primary optic atrophy, though Osler [40] suggests only 10 per cent. This usually develops in the pre-ataxic stage; but it may precede the first symptom of tabes by from two to twenty years, and occasionally does not occur until the late stages of that disease.

Case 5.—Here primary optic atrophy is the first manifestation and tabes is only just commencing (Turtle [52]).

A man, aged 37, had syphilis seventeen years ago. His sight began to fail four years ago, and for the last four months he had shooting pains in the left leg. There was marked primary optic atrophy, most advanced in the left eye. The pupils reacted to light. There was slight Rombergism and ataxia. The tendon reflexes were normal except that the right knee-jerk was diminished.

Case 6 is an example of primary optic atrophy with absent ankle-jerks.

William H., aged 35, contracted syphilis sixteen years ago and gives a positive Wassermann. His sight began to fail two and a half years ago, and his left eye is now quite blind. There is primary optic atrophy in both eyes, the left more advanced. There is some ptosis. His pupils are unequal, eccentric and of the Argyll-Robertson type. He is not ataxic and Romberg's sign is not present, though he cannot stand on one leg with the eyes shut. His knee-jerks are present but the ankle-jerks are lost.

Case 7.—Here the tabes is more marked. As this man has no perception of light the loss of pupil reflex to light may be ignored.

Edward T., aged 27. No history of syphilis, but there is a question whether he is not the subject of congenital disease. He gives a positive Wassermann. He gradually lost his sight nine years ago, and is now quite blind. Primary optic atrophy was the diagnosis of the oculist who saw him at the time. Six years ago he began to suffer from lightning pains. His pupils are unequal, irregular and of the Argyll-Robertson type. Romberg's sign is present, and the ankle-jerks are absent. (This man's wife has suffered from keratitis, but has had no miscarriages.)

Case 8 shows tabes still more advanced.

Edward M., aged 33; acquired syphilis fourteen years ago. Gives a positive Wassermann. Failing sight first symptom. There is primary optic atrophy in both eyes, the pupils are of the Argyll-Robertson type. He suffers from vesical crises, his gait is ataxic, Romberg's sign is present, and the ankle-jerks are lost.

Case 9.—This man is interesting on account of the extreme delay in development of parasyphilis.

George B., aged 66, had syphilis fifty years ago. He gives a positive Wassermann. Pupils unequal and fixed. Primary optic atrophy in the left eye. Paresis of the left internal rectus. Both knee- and ankle-jerks are absent. There is ulnar anæsthesia, and analgesia of the calves.

(*b*) *Primary Optic Atrophy combined with General Paralysis.*

This combination is by no means so common as the last, primary optic atrophy being present in not more than 4 per cent. of pure general paralytic patients; but it is present in a very considerable proportion of tabo-paretics, and of juvenile general paralytics. Most of the latter find their way into idiot asylums, *via* the blind schools, as epileptic imbeciles. Here again we may find one case where primary optic atrophy develops in the course of typical general paralysis, and another where the optic atrophy was the first and most definite manifestation of parasyphilis; the latter being by far the commoner.

Case 10.—Mott [35] records the following example amongst others:—

A girl, aged 15, the subject of hereditary syphilis, was bright and intelligent up to 13. She then developed double primary optic atrophy, and went quite blind. She is now mentally and physically infantile, wet and dirty. Her knee-jerks are unobtainable owing to rigidity of the legs. The pupils do not react to light. She is suffering from progressive dementia.

Case 11.—A woman mentioned by Head [21]:—

E. L., aged 23. The subject of congenital syphilis (Hutchinson teeth, scars at angles of mouth). At 6 years of age she went blind from primary optic atrophy. At 20 she degenerated mentally; from being amenable and industrious, she became careless and incompetent. There is no paresis, the reflexes are normal, but her tongue is slightly tremulous.

(*c*) *Primary Optic Atrophy alone.*

Primary optic atrophy is a disease of fairly frequent occurrence, and although it is often found in the subjects of congenital syphilis, when it is met with in the adult it is not usually looked upon as parasyphilitic, even where there is no suspicion of diabetes or other accepted cause.

The following cases I think strongly suggest its parasyphilitic character; none of them had any symptoms of neuronic degeneration beyond the optic atrophy.

Case 12.—Sidney P., aged 28, had syphilis ten years ago. Gives a positive Wassermann. His pupils are normal, but he has double primary optic atrophy. All his tendon reflexes are normal.

Case 13.—James L., aged 49. No history of syphilis, but he gives a positive Wassermann. He has Argyll-Robertson pupils and primary optic atrophy. His deep reflexes are normal.

Case 14.—William E., aged 40. No history of syphilis, but he has given a positive Wassermann reaction three times. His cerebrospinal fluid shows no lymphocytosis. He has double primary optic atrophy. His pupils are normal, though they react only sluggishly to light. All his reflexes are normal. Indican and glycuronic acid have been found in the urine, but no sugar by any test. He is a very heavy smoker. His wife has specific ophthalmic lesions, old corneal opacities, iritic adhesions, choroidal atrophy, but they may be congenital. She has one healthy child, and has had no miscarriages.

The next two are congenital syphilitic children, with no symptoms beyond primary optic atrophy.

Case 15.—Ellen M., aged 15. Has periosteal nodes and other evidence of hereditary disease. She gives a positive Wassermann, and her cerebro-spinal fluid shows lymphocytosis. Her pupils are dilated and fixed. She has double primary optic atrophy. All her tendon reflexes are normal.

Case 16.—Frederick H., aged 7. He shows evidence of hereditary syphilis, and gives a positive Wassermann. His pupils are normal, reacting sluggishly to light. He has primary optic atrophy. All his reflexes are normal.

Either of these two may of course develop into juvenile tabes or general paralysis, but at present there is no indication of it. In none of these five cases of primary optic atrophy was there anything, remote or immediate, except syphilis, which could be considered the cause of the condition, unless the excess of tobacco in Case 14 be so regarded.

CHAPTER V.—PRIMARY LATERAL SCLEROSIS AS A PARASYPHILITIC MANIFESTATION, EITHER COMBINED OR ALONE.

(a) *Primary Lateral Sclerosis combined with Tabes.*

Instances where signs of involvement of the lateral columns are noted in conjunction with tabes have been diagnosed as postero-lateral sclerosis or ataxic paraplegia. But the tendency has been to assume some syphilitic or traumatic thickening of meninges compressing the lateral columns to account for the paraplegia, and to refuse the combined disorder admission to the jealously guarded parasyphilitic portals. It would seem, however, simpler to explain the precisely analogous degenerations of two neuronic groups, lying side by side in the spinal cord, as due to one primal toxic influence, than to find a separate cause for each.

As with other parasyphilitic amalgamations, the intensity of the components varies within wide limits. So that cases of tabes where there are no more than one or two signs of lateral sclerosis, and of primary lateral sclerosis with very early tabes, come under the same heading as those in which both diseases are well marked. The following cases illustrate varieties of this combination.

Case 17.—In this man with primary lateral sclerosis the sensory disturbance points to the development of tabes in combination.

Robert M., aged 53. Wassermann positive. He denied all venereal disease till told of the significance of this test; he then admitted "gonorrhœa" twenty-five years ago. His pupils are normal, the knee- and ankle-jerks are exaggerated, ankle-clonus is present, and both plantar reflexes are extensor. In addition he has loss of power, with loss of tactile and painful sensations in both legs; there is difficulty in micturition, and weakness of abdominal muscles. Antisyphilitic treatment for a year was not beneficial, and injection of salvarsan gave no result.

Case 18.—Francis M., aged 29. Had syphilis six years ago, and was treated for two years. His cerebrospinal fluid shows lymphocytosis. His first symptom was staggering gait twelve months ago. A few days before admission he was thrown from a van and fell on his back. He was unable to walk for two days, but that passed off. On admission he had pain in the back (D. 12), weakness in the legs, and difficulty in starting micturition. His pupils were unequal but reacted. There was no anæsthesia. His gait was inco-ordinate and spastic. Romberg's sign was present. His knee-jerks were exaggerated, ankle clonus was present, and Babinski's sign was marked. There were no intention tremors nor nystagmus. Antisyphilitic remedies had no effect on his condition, although the pain in the back, which was probably due to the fall, disappeared.

Case 19.—William J., aged 48, had syphilis fourteen years ago. Wassermann positive, and lymphocytosis present in the cerebrospinal fluid. Four years after infection the patient was exposed to considerable hardship in the Boer War, and his right leg became weak and "dragged." This remained much the same for three years; then he had a course of antisyphilitic treatment without improvement. Six years later he gave a negative Wassermann, and was treated with Faradic baths. Twelve months after that the Wassermann reaction was positive, and he came into hospital for salvarsan treatment. The pupils are normal. Knee-jerks are absent. Plantar reflexes extensor. His gait is inco-ordinate, Romberg's sign is present, both legs are analgesic but not anæsthetic; the right leg is rather wasted, but there are no trophic lesions. He has lightning pains. No ulnar anæsthesia. A fortnight after salvarsan injection the Wassermann reaction was negative, although it had been positive a month before. The importance to be attached to this, since the interval is so short, is doubtful.

(b) *Primary Lateral Sclerosis combined with General Paralysis.*

Cases have been recorded where general paralysis has developed in a patient already suffering from primary lateral sclerosis (Osler [41]), and certainly general paralytics may, and often do, exhibit exaggerated reflexes, whilst sometimes Babinski's sign is well marked.

Case 20.—Frank L., aged 28, had syphilis six years ago; he gives a Wassermann reaction with both serum and cerebrospinal fluid. The latter shows lymphocytosis and gives the precipitation tests. He has the mental symptoms and tremors of general paralysis. His pupils are irregular, but react. His gait is normal; his knee-jerks are present; there is no ankle clonus, but the plantar reflexes are extensor.

Case 21.—Thomas B., aged 39. He gives no history of syphilis, but the Wassermann reaction is positive, and the cerebrospinal fluid responds to the precipitation tests. He has the mental symptoms, slurred speech and tremors of general paralysis. There is marked intention tremor in the right arm. The elbow-jerks are absent; the pupils are unequal and irregular, but react. There is slight ptosis. His gait is unsteady and inco-ordinate; his knee-jerks are exaggerated, ankle clonus is present, and the plantar response is extensor.

Case 22.—Here is a case, recorded by Poynton [44], in which general paralysis and primary lateral sclerosis are combined in a child, the subject of congenital disease.

A girl, aged 11, with Hutchinson's teeth and patches of choroiditis. She has degenerated mentally, morally, and physically for two years, becoming dirty and silly. Her tongue is tremulous. Her pupils are unequal and fixed. She is unable to walk on account of spastic paraplegia, which is more marked in the left leg than the right. The upper extremities are normal, but the deep reflexes in the legs are increased, and Babinski's sign is present in the left foot.

(c) *Primary Lateral Sclerosis combined with Primary Optic Atrophy.*

This will at first sight be diagnosed as disseminated sclerosis. But instances occur in which there is primary optic atrophy with spastic paraplegia or Babinski's sign, and no other sign of dissemination, in patients past the usual age for disseminated sclerosis. These may well be really a combination of two of the rarer forms of parasyphilis and not a haphazard insular degeneration at all. Both the cases below, in illustration of this amalgamation, came under observation before Wassermann's reaction had assumed importance.

Case 23.—Henry C., aged 69, had syphilis forty years previously. His pupils were normal, there was ptosis and ophthalmoplegia of the external rectus, both on the right side. His vision was blurred and he proved to have double primary optic atrophy. Romberg's sign was present, his left knee-jerk was exaggerated, the right one diminished, and Babinski's sign was present.

Case 24.—Agnes N., aged 41, a married woman, giving a history of "vaginal trouble" some years previously. She had double primary optic atrophy. The pupils were normal, there was no nystagmus. The knee-jerks were exaggerated, ankle clonus was present, and the plantar reflexes were extensor.

(d) *Primary Lateral Sclerosis alone.*

Some cases of primary lateral sclerosis give a history of syphilis, but no reliance can be placed on statistics in this condition unless Wassermann's test has been applied or a *post-mortem* examination made, for so many cases diagnosed as primary lateral sclerosis are found *post-mortem* to be secondary to cerebral tumour or other unsuspected cause. It is probable that nearly every, if not every, instance of uncomplicated primary sclerosis of both lateral columns is parasyphilitic; but such examples are not common.

Case 25.—Alfred D., aged 64, had syphilis forty years ago and gives a positive Wassermann. Disease began a year ago with weakness of the legs. Six weeks ago paralysis of the right external rectus showed itself. His pupils are normal. His gait is spastic; Achillis jerks brisk; Babinski's sign is present.

Case 26.—Here is a case of early primary lateral sclerosis with Argyll-Robertson pupils.

James T., aged 43, had syphilis twenty-five years ago and now gives a positive Wassermann. His pupils are unequal, irregular, eccentric and of the Argyll-Robertson type. There is slight ptosis. The ankle-jerks are exaggerated with a tendency to clonus. The plantar response is flexor in the right foot and unobtainable in the left. He cannot stand on one leg with the eyes shut. There is spasticity of the ankle-joints with a tendency to stand always on tiptoe.

Case 27.—Winifred E., aged 29, a married woman who has had one miscarriage and gives a positive Wassermann reaction. The elbow-, knee- and and ankle-jerks are all exaggerated and Babinski's sign is present. Her eyes are normal, and there is no nystagmus nor any other sign of insular sclerosis.

Case 28.—Edward C., aged 38. No history of syphilis but gives a positive Wassermann. His pupils are normal. The legs are spastic, knee-jerks exaggerated, ankle clonus present, plantar reflexes extensor.

Case 29.—James H., aged 54, had syphilis twenty-five years ago. Wassermann reaction positive. Pupils are normal. There is slight tremor of the tongue. Romberg's sign is present. His knee-jerks are increased, ankle clonus is present and the plantar reflexes are extensor.

Case 30.—Here is an interesting case, recorded by Grainger Stewart [49] as "chronic syphilitic meningitis with compression of the cord," which I think is more probably an example of parasyphilis of the variety under consideration, for the pupils do not react to light, though they do to accommodation. There is also some sensory disturbance which may be the first sign of the supervention of tabes.

A man, aged 64, had syphilis forty-six years ago. Ten years ago he fell unconscious in the street, the unconsciousness lasting fifteen minutes. There was no paralysis or other after-effect from this incident, and it is doubtful whether it has any connection with the ultimate condition. Five years later his legs became stiff and he developed into an example of spastic paraplegia. The knee- and ankle-jerks are exaggerated, ankle clonus is present and the plantar response is extensor. The pupils are of the Argyll-Robertson type. Motor weakness is slight. The abdominal and epigastric reflexes are absent, and there is slight diminution of all forms of sensibility below the fourth dorsal segment. Nothing abnormal is found in the spine.

CHAPTER VI.—PROGRESSIVE MUSCULAR ATROPHY AS A PARASYPHILITIC MANIFESTATION, EITHER COMBINED OR ALONE.

(*a*) *Progressive Muscular Atrophy combined with Tabes.*

Quite early in this paper I referred to Dejerine's [8] estimate that 20 per cent. of tabetics exhibit some form of muscular atrophy, and to the fact that progressive muscular atrophy is becoming more and more frequently recognized in France as a parasyphilitic manifestation. Still as a rule the muscular atrophy is looked upon as one of the less frequent symptoms of tabes, or else it is saddled on to one or other of the etiological pack-horses, usually "hard work." Kinnier Wilson [53], however, in recording the following case, says that he considers "tabetic muscular atrophy is neither a symptom nor a complication of tabes, but an associated condition of syphilitic origin."

Case 31.—A man, aged 37, had syphilis twenty-two years previously. He had been troubled with lightning pains for ten years, girdle pains for nine years and wasting of the small muscles of the hands (starting in the right) for seven years. He had gastric crises, and experienced abnormal fatigue in the legs. His pupils were of the Argyll-Robertson type, the deep reflexes absent. There was extreme wasting of the thenar and hypothenar muscles, with no reaction to faradism or galvanism. The interossei were less wasted; there was no great wasting in the arms, though they were weak. In the legs all the muscles, particularly the anterior tibial groups, were small and weak. Sensation of pain was impaired in the ulnar distributions, and almost lost in the legs. There was loss of tactile sensibility over the trunk and legs. His right ankle was an incipient Charcot joint. The pathological report of this case records that there is great reduction in the cells of the anterior horns, the change being atrophic or sclerotic. What cells remain are mostly shrunken. The side where the muscular atrophy was most obvious (i.e., the right) shows the greater changes in the cord.

Case 32.—This is an instance of early progressive muscular atrophy in a tabetic patient.

George S., aged 44, gives no history of syphilis, but the Wassermann reaction is positive. His pupils are irregular and of the Argyll-Robertson type. His Achillis-jerks are absent. He has perforating ulcers, rectal crises and anæsthesia of the bladder (he does not know when it is full). The tongue is tremulous, and there is marked weakness and wasting of the intrinsic thumb-muscles of both hands.

Case 33.—Here is a case where the lower neuron degeneration is affecting the bulbar nuclei.

Charles H., aged 36. No history of syphilis, but he gives a positive Wassermann. He has Argyll-Robertson pupils. The ankle-jerks are absent and Romberg's sign is manifest. He has difficulty in swallowing owing to paralysis of the muscles of the soft palate. (No history of diphtheria could be elicited; the patient denied having a sore throat.)

(b) *Progressive Muscular Atrophy combined with General Paralysis.*

I have met with well-marked cases of this combination. As a rule, when muscular atrophy occurs in general paralysis of the insane it is considered as an unusually marked example of the weakness which comes on in the ordinary course of that disease.

Case 34.—Henry P., aged 34, had syphilis eighteen years ago, and gives a positive Wassermann and the cerebrospinal precipitation tests. He shows the mental symptoms, tremors and slurred speech of general paralysis. There is slight ptosis, and the pupils are unequal, irregular and of the Argyll-Robertson type. His gait is unsteady, and his knee-jerks are absent. There is extreme wasting of all muscles (most marked in the interossei) of the right hand and of the same shoulder. All the muscles, except the interossei and lumbricales of the right hand, react to faradism and galvanism, though both are diminished, especially in the right arm and shoulder, and particularly in the right infraspinatus. The interossei of the left hand are also affected.

Case 35.—James Q., aged 50, admits syphilis, but does not know the date. Wassermann reaction positive, cerebrospinal fluid gives precipitation tests, and shows lymphocytosis. There are tremors of the tongue and lips. He is very grandiose and happy. He has slight right-sided ptosis; his pupils are unequal, irregular and fixed. His knee-jerks and all other deep reflexes are lost, as also are the cremasteric and abdominal. The interossei of both hands are wasted, and there is some motor impairment of the right arm.

(*c*) I have not encountered a satisfactory instance of the combination of progressive muscular atrophy with primary optic atrophy.

(*d*) *Progressive Muscular Atrophy combined with Primary Lateral Sclerosis.*

Here we have the condition known as amyotrophic lateral sclerosis; or, when the degeneration extends to, or occurs at, the upper end of the cord and medulla, progressive bulbar paralysis. If the symptom-complex comprising progressive muscular atrophy, amyotrophic lateral sclerosis and progressive bulbar paralysis be considered as one primary degeneration of the motor neurons, both upper and lower, we see how cases may vary according to what point in the group is first attacked, and to what extent the disease spreads thence throughout the group. It may begin in the anterior cornual cells and confine itself to that system, giving simple progressive muscular atrophy; or it may extend to the pyramidal tracts, giving amyotrophic lateral sclerosis; and later the bulbar nuclei and the hypoglossal nerve may be involved, thus adding bulbar paralysis, which, fortunately for the victim, as a rule rapidly carries him off. But the trouble sometimes starts with bulbar paralysis, and may show evidence, before the patient dies, of downward spread.

In 1850, Aran [1] first described progressive muscular atrophy starting in the intrinsic muscles of the hands. In 1859, Duménil [9] noted progressive bulbar paralysis with atrophy of the hypoglossal nerve, and regarded it as a form of progressive muscular atrophy. In 1872, Charcot [6] described amyotrophic lateral sclerosis, considering it also as an extension of progressive muscular atrophy.

With regard to the etiology of these varieties of motor-tract degeneration, Dana [7] and Merle [27] urge syphilis as the essential cause, whilst Wilson [54] (in 1907) considers lead poisoning the commonest factor, and thinks that in some cases syphilis can be excluded. Gowers [17] thinks there is some evidence of heredity. The points in favour of parasyphilis are the age-incidence (in the parasyphilitic decade—the fourth), the greater frequency with which men are attacked than women, and the fact that Argyll-Robertson pupils are sometimes associated.

Case 36.—William V., aged 52, does not admit syphilis, but gives a positive Wassermann reaction. He gives a four years' history of general progressive weakness and loss of control of the legs: "Feet catch in everything." He complained that his feet and legs were numb, and of cramps in the feet, legs, thighs and hands. There is no absolute paralysis, but general paresis. His tongue is not tremulous, but his speech is altered and his voice falsetto. The pupils are normal and react, if anything, better to light than to accommodation. Sensation is unimpaired. His knee-jerks are present: the left ankle-jerk is increased, the right absent. The plantar reflex is extensor in the left foot, unobtained in the right. The cremasteric and abdominal reflexes are present. There is well-marked wasting of both thenar eminences, and he cannot oppose the thumb and little finger. There is some wasting noticeable in the left leg.

Case 37.—William B., aged 50; he had syphilis thirty years ago, and has been troubled for nineteen months with weakness of the left hand, for six months with the same in the right hand, and lately with weakness of the left leg. In the left hand there is marked wasting and loss of power in all the intrinsic muscles; also in the forearm, both flexors and extensors; there is very little movement in the elbow-joint, and practically none in the shoulder. The atrophy in the right hand is much less marked. Reaction of degeneration is present in all the affected muscles, and is complete in the interossei of the left hand. The legs are weak, but show no obvious wasting. His knee-jerks are exaggerated; both ankle-clonus and Babinski's sign are present.

(*e*) *Progressive Muscular Atrophy alone.*

As a parasyphilitic manifestation progressive muscular atrophy is certainly most often met with in combination; but the fact that the knee-jerks may be lost in this condition quite early has probably led to a considerable proportion of these cases being diagnosed as locomotor ataxia with marked muscular symptoms.

Case 38 shows this liability, as the tendon reflexes are absent, although the muscular atrophy is confined, clinically, to the upper extremities. Probably some change is present in the cord lower down, some shrinkage of anterior cornual cells.

Thomas F., aged 53, had syphilis thirty-five years ago. Wassermann reaction positive. His pupils are irregular but react, though very faintly only, to light. The deep reflexes are lost. There is no ataxy. Wasting is evident in both upper limbs in the interossei, thenar, and hypothenar eminences. the flexors and extensors of the forearms, the muscles of the upper arms and shoulders. The legs are unaffected.

Case 39.—Joseph A., aged 50, had syphilis thirty years ago. His pupils are unequal but react. The right knee-jerk is absent, the left present. The thenar and hypothenar eminences are wasted, especially of the right hand, also the interossei, the flexors of arms and upper arms, the supra- and infra-spinati and the lower part of the pectoralis major. The right thigh is also much wasted.

W. Harris [18], treating of syphilis of the spinal cord, mentions cases of chronic or subacute poliomyelitis due to syphilis. These he says are "generally mistaken for progressive muscular atrophy." He refers to three cases, recorded by Max Nonne, in which the upper extremities only were affected; and three by J. Hoffmann. But Hoffmann [22], at all events, is one of those who recognize progressive muscular atrophy as a parasyphilitic manifestation. Harris also describes the following case of his own:—

Case 40.—A woman (age not given), with a definitely positive Wassermann, had pain in the left upper arm as the first symptom of disease, followed by paralysis of the deltoid. A year later her right wrist dropped, and the right shoulder became paralyzed. A year later there was almost complete paralysis of both deltoids, biceps, spinati, and extensors of the forearm, with reaction of degeneration. There was no sensory disturbance; all the deep reflexes except the jaw-jerk were absent, and the pupils reacted sluggishly to light.

The Wassermann reaction and the slowly progressive nature of the complaint suggest a diagnosis of parasyphilitic progressive muscular atrophy. I fail to see on what grounds a special class need be devised for "Cases generally mistaken for progressive muscular atrophy."

Rose et Rendu [46], in the interesting article already referred to, describe two cases in which no cause but syphilis could be suggested. In the first they hold that, in spite of some exaggeration of reflexes and a tendency to ankle clonus, it is a case of pure progressive muscular atrophy. But these signs should rather be held to point to some involvement of the pyramidal tracts, and as suggesting the development of the case into amyotrophic lateral sclerosis.

Case 41.—A man, aged 42, except for syphilis at 18, never had any illness. He was treated for two years, and married at 26. His wife's first pregnancy resulted in miscarriage. Some difficulty in using his hands appeared six years ago. This paresis progressed, and two years later spread to the arms successively. He has no pain, but some alteration of sensibility to cold. No urinary trouble, but loss of sexual power for the last year. The thenar and hypothenar muscles of both hands are very markedly atrophied, also the first interossei. Atrophy not so marked in the forearms, affecting the extensors and supinators only in the right, but the flexors, too, in the left. The elbow-jerks are exaggerated. The legs are unaffected, except that the reflexes are somewhat exaggerated, with a tendency to ankle clonus on both sides. Plantar response flexor. The right cremasteric reflex is absent. The pupils are of the Argyll-Robertson type; and there is an intense cerebrospinal lymphocytosis.

The second case differs from the above in that all the deep reflexes are absent, and is a pure example of progressive muscular atrophy alone.

Case 42.—A man, aged 34, had syphilis at 21. Three years later he had lightning pains. Six years after infection the right hand began to get weak and waste, the thumb being first affected. Four years later the left hand followed suit and the forearms and arms became involved. There was progressive loss of power before the atrophy appeared. The trophic changes are confined to the upper limbs, being most marked in the thumb-muscles of the right hand, and the interossei of the left. The right arm is almost useless, the left not so advanced. The deep reflexes are absent in all four limbs, the superficial ones remaining. There are no abnormalities of sensation; no ataxia; Romberg's sign is not present, and there are no sphincter troubles. The pupils are unequal, and are described as "incomplete Argyll-Robertson." There is no optic atrophy. The cerebrospinal fluid shows lymphocytosis. No benefit has accrued from anti-syphilitic treatment.

CHAPTER VII.—CASES WHERE MANIFESTATIONS OF DEGENERATION IN MORE THAN TWO NERVE TRACTS OCCURRED IN ONE INDIVIDUAL.

In studying these parasyphilitic nervous diseases one is constantly aware of a suspicion that more tracts are involved than is manifested at first sight. Some abnormality of sensation, some failure of vision, some change in moral or intellectual characteristics, some lately developed jerkiness of movement, some loss of power in the hands, or an alteration in the voice, may attract the attention and suggest that the decay is not confined to one or even two communities of neurons.

For this reason it is often very difficult to classify a case; and having classified it, one is frequently tempted to remove it to some other group. Parasyphilis of the nervous system must be considered, in fact, as one polymorphic disease with many different manifestations. The clinical picture is almost kaleidoscopic in its infinite variety. Taking only the five manifestations dealt with in this paper, the diagrammatic representation of their combinations in pairs is well-nigh confusing, and would be entirely so were the multiple conditions now to be considered indicated.

Yet, in a full consideration of parasyphilis of the nervous system, room must probably be found for certain neurasthenias, dystrophies, non-developments and epilepsies, with their associations.

Of multiple manifestations one would naturally expect the greater number to be based on tabo-paresis; and such is the case. I shall not describe more than one instance of each variety.

Case 43.—Tabo-paresis with primary optic atrophy.

John S., aged 50, denies syphilis but has a scar on the glans penis. He gives a positive Wassermann both with blood and cerebrospinal fluid; the latter further shows lymphocytosis and gives the precipitation tests. He has the mental symptoms of general paralysis, with slurred speech and tremors of the tongue, lips and hands. His gait is unsteady, and his knee-jerks are absent. His Argyll-Robertson pupils are irregular in outline, and there is primary optic atrophy in both eyes, especially in the left.

Case 44.—Tabo-paresis with primary lateral sclerosis.

George C., aged 33. He had syphilis thirteen years ago and gives a positive Wassermann reaction. He now shows the mental symptoms of general paralysis: his speech is defective, his tongue tremulous, his pupils irregular and of the Argyll-Robertson type. He does not exhibit Romberg's sign, but both his knee- and ankle- jerks are absent. Finally the plantar reflex is extensor in both feet.

Case 45.—Tabo-paresis with progressive muscular atrophy.

George E., aged 45. No history of syphilis was obtained, but he gave a positive Wassermann, and his cerebrospinal fluid gave the precipitation tests. He has the mental signs of general paralysis of the insane with tremulous tongue and lips, and slurred speech. In addition there is ptosis on the left side; his pupils are unequal, irregular and of the Argyll-Robertson type. His gait is ataxic, and his knee-jerks are absent. There is marked progressive trophic wasting of the right thigh and calf-muscles.

Case 46.—General paralysis of the insane with amyotrophic lateral sclerosis.

Sophie P., aged 43. No history of syphilis, but her cerebrospinal fluid gave both the precipitation tests and the Wassermann reaction. She has the mental signs, tremors, and defective speech of general paralysis. Her pupils react to light and accommodation, though very slightly to the former. Her legs are inco-ordinate. The knee-jerks are present, and there is ankle clonus and extensor plantar reflex on the left side. There is great progressive muscular wasting of both arms and legs.

Case 47.—Tabo-paresis with primary optic atrophy and primary lateral sclerosis. Here four nerve-tracts show evidence of decay. This man had a very severe attack of syphilis, with troublesome sores all over the body.

John W., aged 46, had syphilis twenty years ago; his wife has had numerous miscarriages. He gives a double Wassermann reaction and his cerebrospinal fluid also exhibits lymphocytosis and the precipitation tests. He is demented, his tongue and fingers are tremulous. He is inco-ordinate, though his gait is fair. The tendon reflexes in both legs and arms are absent. Babinski's sign is present. He has double primary optic atrophy, and his pupils are unequal, irregular and of the Argyll-Robertson type.

Tooth and Howell [51] publish an exhaustive account of a very severe case of amyotrophic tabes from the point of view that the tabes and muscular atrophy are due to two distinct causes, though the separate and distinct cause of the latter is not clearly indicated. I bring my series of cases to an end with an abstract of this one because it appears evident to my mind that it is an instance of parasyphilis of the nervous system exhibiting signs of degeneration in four separate nerve-tracts. One of these, however, the pyramidal, was not indicated during life, or was overshadowed by the intensity of the other troubles.

Case 48.—Tabes with primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy.

A man, aged 35, had syphilis sixteen years before. For sixteen months there has been progressive difficulty in walking and numbness of the feet. He is mentally bright, but physically troubled with lightning pains, girdle pain, gastric crises, difficult micturition, right-sided ptosis, and failing vision, especially in the left eye. Articulation lisping. Tongue tremulous, left half atrophied. Unequal Argyll-Robertson pupils. Discs distinctly suggestive of primary optic atrophy. Almost complete ophthalmoplegia of both eyes. Some paresis of lips. Hearing defective in both ears. Left masseter muscle wasted. Muscular power in arms and trunk fair, legs very weak and atrophied, the right more so than the left. Can only just stand with support, and attempts to walk only result in disordered ataxic movements. Muscle-pain sense lost, joint-sense defective. Analgesia over greater part of face and body, most marked in ulnar distribution and outer sides of legs. Marked inco-ordination in the arms as well as legs. All the above symptoms were progressive, and the right side of tongue, the right masseter muscle, and both temporal muscles became involved in the atrophy, and deglutition became increasingly difficult.

Pathological examination showed that the third, fifth, sixth, and twelfth cranial nerves were wasted. The pia arachnoid was a little thicker over the posterior columns in the cervical and upper dorsal region. Both posterior and anterior nerve-roots were small. The anterior cornual cells were diminished in number, and those remaining were shrunken. The degeneration of posterior columns was typical of tabes, and there were slight degenerative changes in the lateral columns. The affected muscles showed changes identical with those of progressive muscular atrophy, though the eye-muscles were very little altered.

SUMMARY.

There is no doubt that in the vast majority of cases of tabes and general paralysis of the insane syphilis is the essential cause. They are parasyphilitic nervous diseases.

There is evidence that at all events some cases of primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy, are parasyphilitic too. A history of syphilis or a positive Wassermann reaction, and in some instances the *post-mortem* examination, point to this being so.

In tabes and general paralysis there is degeneration of certain neuronic tracts or groups; and degeneration of precisely the same character in other neuronic groups produces primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy.

Combinations of all three with tabes or general paralysis of the insane, or with both, or amongst themselves, are so frequent that it is difficult to withstand the conclusion that their essential etiological factor is the same, more especially since it is conceded that syphilis has a great affinity for the nervous system.

If it be allowed that the neuronic degeneration of primary optic atrophy, primary lateral sclerosis or progressive muscular atrophy when combined with that of tabes or general paralysis is due to syphilis, it cannot be denied that such degeneration, occurring uncombined, may still be parasyphilitic.

The Argyll-Robertson pupil is recognized as a symptom of tabes and general paralysis, in other words it is a parasyphilitic manifestation. It is found also with primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy.

If the question of antecedent syphilis were carefully investigated in every case of primary optic atrophy, primary lateral sclerosis and progressive muscular atrophy, or better still if every case were subjected to Wassermann's test as well, I believe that an accumulation of evidence, entirely analogous to that obtained in determining the etiology of tabes and general paralysis, would soon be at hand, and that these three diseases, at present wandering in the Wilderness of Undiscovered Causes, would take their rightful place amongst the rarer manifestations of parasyphilis of the nervous system.

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PUBLICATIONS RECENTLY RECEIVED.

[*Notes on a book under this heading do not preclude a subsequent review.*]

The Pituitary Body and its Disorders. By HARVEY CUSHING, M.D., Professor of Surgery, Harvard University. Pp. 341, with 319 illustrations. Philadelphia and London: Lippincotte, 1912.

This remarkable work is the fruit of a series of researches carried out by Professor Harvey Cushing in conjunction with his colleagues and assistants in the Johns Hopkins Hospital. A short account is first given of the anatomy and physiology of the pituitary body, of which the posterior portion pours its secretion into the cerebrospinal fluid, whilst the anterior part acts with the other ductless glands. Then cases of disease are analyzed and shown to be due to excess, to diminution, or to defective pituitary activity; those patients in whom the secretion has been in excess grow to a huge size and undergo premature sexual development, while diminished activity leads to small size, adiposity, and sexual infantilism. Many cases, however, especially those due to neoplasms of the hypophysis, show first a period of excessive, followed by one of defective, activity of the glands: into this group fall some instances of acromegaly.

But the pituitary body is one of the ductless glands, and its disturbed activity may be associated with those of other similar organs. Hence arises the so-called "polyglandular syndrome," indicating that it is difficult to tell which of the glands is primarily at fault; the patient may show signs pointing to thyroïd, adrenal and pituitary insufficiency.

The pathology, nature, and clinical character of tumours within the sella turcica are considered, and the various surgical and therapeutic measures for their relief are dealt with fully.

The book is one so full of interest, and the author's conclusions are so illuminating, that we cannot do justice to it in a short notice.

Die Wassermann'sche Reaktion mit besonderer Berücksichtigung ihrer klinischen Verwertbarkeit. Von Dr. HARALD BOAS. S. 186. Berlin: Karger, 1911.

Although not directed primarily to the problems of nervous disease, every neurologist interested in the Wassermann reaction should read this work. After a clear and concise account of the reaction and its modifications, its value is established by a large series of examinations in control cases. Then Dr. Boas deals with the reaction in primary, in secondary, in tertiary and in latent syphilis. A chapter is devoted to each of the following conditions: tabes dorsalis, dementia paralytica and congenital syphilis. He deals with the influence of treatment on the reaction and with its practical significance from the therapeutic aspect.

Surgery of the Brain and Spinal Cord based on Personal Experience. By Prof. FEDOR KRAUSE, M.D., English adaptation by Dr. MAX THOREK. Vol. ii, with 94 figures in the text; vol. iii, with 42 figures in the text. The pages, numbered consecutively from the beginning of vol. i, reach 1197. London: H. K. Lewis. No date.

The first volume of this translation of Professor Krause's admirable work appeared in 1910 and was noticed in BRAIN, vol. xxxiii, page 267. The book is a personal record of one man's work; each condition of the central nervous system likely to come to operation is passed in review and one or more instances from the author's experience are fully described and illustrated. Thus, the present volumes deal with epileptiform attacks, Jacksonian epilepsy and the results of excision of the cortex. New growths of the brain, in all important situations, are considered on the basis of 109 cases which came to operation; the description of signs and symptoms is usually rather short and rigidly directed towards a diagnosis. The third volume is mainly occupied with an interesting series of tumours of the spinal cord, and other conditions which may simulate a new growth such as meningitis serosa acuta circumscripta.

Throughout, the illustrations, and especially the coloured plates, are excellent, in fact they form a valuable atlas of the pathology during life of the central nervous system. The English of the translation leaves much to be desired.

Die akute Poliomyelitis bzw. Heine-Medin'sche Krankheit. Von Dr. IVOR WICKMAN. S. 108. Mit 12 Textabbildungen und 2 Tafeln. Berlin: Springer, 1911.

This pamphlet, giving in short compass an account of acute poliomyelitis, is a separate publication of Dr. Wickman's article in Lewandowsky's "Handbuch der Neurologie." It forms a most useful compendium of our present knowledge and of recent researches on this disease for those who are particularly interested in poliomyelitis.

Arbeiten aus dem Pathologischen Institut der Universität Helsingfors (Finland). Herausgegeben von Prof. Dr. E. A. HOMÉN. Band iii, Hefte 2-4, S. von 91 bis 607; mit 30 Tafeln. Berlin: Karger, 1911.

This volume of researches is occupied with experiments on tuberculosis of the peripheral nerves, by Professor Homén; of the liver, by Dr. Wallgren, and by a monograph on experimental tuberculosis of the meninges and brain, by Dr. Fieandt. The plates are excellent.

Ergebnisse der Neurologie und Psychiatrie. Redigiert von Prof. Dr. H. VOGT und Doz. Dr. R. BING. Erster Band, erster und zweiter Hefte, S. 452; mit 38 Abbildungen. Jena: Fischer, 1911.

This interesting volume starts with an account by Dr. Isserlin of the progress in psychotherapy during the last few years; a clear and remarkably fair summary is given of the treatment adopted by the various schools, with, in each case, a short statement of the views upon which it is based. This is followed by a review of the pathogenesis and symptomatology of cerebellar diseases by Professor Mingazzini. Dr. Spielmeyer deals with dementia paralytica, tabes dorsalis and sleeping sickness from the standpoint of etiology and pathology, and Dr. Kleist gives an interesting account of the present views on apraxia. We hope that these excellent short monographs will be continued, as they supply a want amongst neurologists who are not directly working at the particular subject with which they deal.

The Psychology of Insanity. By BERNARD HART, M.D. Pp. 176. Cambridge: University Press, 1912.

It is difficult to speak too highly of this little book, which forms one o the Cambridge manuals of science and literature. The author has succeeded in displaying the psychological conception of abnormal mental states so simply and clearly that it can be grasped by anyone; and yet he has avoided the crudities which overload the work of most of the psycho-analytical school. Dissociation, the nature of complexes, conflict, repression and projection are all explained, and instances are given from normal and abnormal mental states. This is one of the best of an admirable series and can be recommended to all who are interested in the problems presented by insanity.

Hypnosis and Suggestion. By W. HILGER, M.D. Translated by R. W. FELKIN, M.D. With an Introduction by Dr. VAN RENTERGHEM (Amsterdam). London: Rebman. No date.

Like most works on this subject, Dr. Hilger's book begins with a somewhat elaborate introduction on the history and nature of hypnosis. This is followed by chapters on suggestion and will, the effect of suggestion on sensation and on disturbances of reflex activity. Many cures are cited, but the clinical instances are poorly related, and the trail of the example taken from "Common Knowledge" is over the book.

The Feeble-minded. By E. B. SHERLOCK, M.D., D.P.H. With an Introduction by Sir H. B. DONKIN, M.D. Pp. 327. London: Macmillan, 1911.

The author begins with two chapters devoted to the nature and basis of mind. He then passes to the feeble mind and the anatomical abnormalities of the brain with which it is associated. The causes and varieties of feeble-mindedness are then described, and in a final chapter he considers the methods of dealing with the feeble-minded.

Neurasthenia. By GILBERT BALLET. Translated from the Third French Edition by P. CAMPBELL SMITH, M.D. Third Edition, illustrated with 7 figures. London: Kimpton, 1911.

This is a good translation of Professor Ballet's work on neurasthenia, and gives a full description of this disease from the point of view of a French clinician. The leading symptoms are described in detail, but sometimes, as in the case of traumatic neurasthenia, the description is scarcely adequate in length. Psychasthenia is wisely eliminated, and the author insists on the necessity for exact diagnosis. The second half of the book is devoted to methods of treatment.

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Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I. to XXIII. inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

[FEBRUARY, 1913.]

BRAIN.

PART III., VOL. 35.

Original Articles and Clinical Cases.

ON A PEDIGREE SHOWING BOTH INSANITY AND COMPLICATED EYE DISEASE: ANTICIPATION OF THE MENTAL DISEASE IN SUCCESSIVE GENERATIONS.[1]

BY E. J. LIDBETTER,
General Relieving Officer, Parish of Bethnal Green, London,
AND
E. NETTLESHIP, F.R.S.

PART I.—A PEDIGREE SHOWING BOTH INSANITY AND COMPLICATED EYE DISEASE.
PART II.—OTHER CASES OF ANTICIPATION IN SUCCESSIVE GENERATIONS.
PART III.—CASES MORE OR LESS COMPARABLE WITH THE SERIES IN PART I.
CONCLUSIONS.

PART I.—A PEDIGREE SHOWING BOTH INSANITY AND COMPLICATED EYE DISEASE.

THE pedigree, fig. 1, forming the basis of the present paper has been already published in a less complete form by Mott, from data supplied by one of us (E. J. L.), as fig. 9, in his article, "The Inborn Factors of Nervous and Mental Diseases," in BRAIN, vol. xxxiv, p. 73 (1911). Further investigations made since that date have enabled the present writers not only to add considerably to the pedigree and give fuller information about many of its members, but to record the condition of the eyes in most of those originally marked as "blind" in Mott's diagram, and of six others in whom ophthalmoscopic examination has disclosed lesser degrees of similar abnormality.[2]

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[1] Part I is by Mr. Lidbetter and Mr. Nettleship, whilst the latter author is responsible for Parts II and III.

[2] We are under obligations to the following gentlemen for their kindness in sending us notes of many of the cases in the pedigree, and for facilities for examining the eyes of those now living in asylums or schools: Dr. H. K. Abbott (Hants Asylum, Knowle, Fareham),

The result was quite unexpected, showing as it does an association between mental deficiency and ocular defects, the latter being partly developmental, partly morbid. The pathological changes are chiefly detachment of the retina, based upon disease of the choroid, but with iritis and secondary cataract in some cases. Both the mental and the ocular conditions are hereditary. Such an association has not been described before as far as we know. Consideration of the details of the various cases seems to us to make it probable that the ocular and the mental defects are due to a common underlying cause, and do not stand to one another either as cause and effect or as accidental coincidences. Nor does it seem probable that the choroiditis and consequent retinal detachment can be attributed to the low or very moderate degrees of myopia found in certain of the patients (V, 5, 14, 15, 16, 18 and 20), and that was also probably present in IV, 13; the myopia itself was more likely a manifestation of the same congenital imperfection of either the scleral or choroidal tissues that led to actual disease in the early life of some of the individuals. As the subject has not yet attracted much attention, we make no apology for presenting the facts with an amount of detail that might otherwise have been unnecessary.

The ocular changes in the present series are absolutely different from any of those with which we are familiar in cases of cerebral and spinal disease; neither optic neuritis, optic nerve atrophy, alterations of the pupillary reflexes, nor ocular palsies have been observed. With the doubtful exception of the man IV, 27, thought to be suffering from general paralysis of the insane, whose case is described below at p. 204, syphilis, whether acquired or congenital, does not seem to have been a factor in causing either the mental or the ocular degeneracies. Tubercle is known as the cause of death in two only of the affected stock, and tubercular joint disease as having occurred in one other, but these numbers make no pretence to completeness. Alcoholic intemperance was sufficiently marked in some half dozen (III, 2, 5, 10, 18; IV, 10, 13), to be noted in the records of the Asylums and Poor Law Institutions of which, at one time or another, they were inmates and

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Dr. Percy J. Bailey (Hanwell Asylum), Dr. E. Faulks (Bexley Asylum), Dr. Robert Jones (Claybury Asylum), Dr. David Ogilvy and Dr. E. Mapother (Long Grove Asylum, Epsom), Dr. E. B. Sherlock (Fountain Asylum, Tooting), Dr. T. E. K. Stansfield (Bexley Asylum), Dr. C. K. Bowes (Herne Bay), Mr. Elmore Brewerton (London), Mr. Treacher Collins (London), Dr. Bradley Figgis (Brighton), Mr. N. Bishop Harman (London), Mr. W. S. Inman (Portsmouth), Mr. F. A. C. Tyrrell (London), Dr. H. Maturin (Winchfield), Dr. Ealand (Farnham), Dr. John H. Ilos (Starcross), and Mr. Daffyd Thomas (Clerk to the Guardians Bethnal Green).

this number, too, is of course the minimum. No consanguineous marriages are known. Of the individuals whose age at, or cause of death has not been ascertained, and who are not known to have had any defined mental or bodily disease, a large proportion of the adults of both sexes have been recipients of Poor Law relief of one sort or another for various periods. It cannot be doubted that the great majority of these persons, omitting cases of accidental sickness and of disablement from old age, became paupers because they were not well enough endowed mentally, physically, or in both respects, to compete successfully in life.

Although we do not know precisely when the ocular degeneration or disease began in those affected by it, the histories and examinations show that it certainly occurred early in life in several of them, whilst the persistence of the later fœtal structures (pupillary membrane and hyaloid artery) in several makes it probable that the whole of the abnormalities, ocular and cerebral alike, began as intra-uterine arrests. There has been no clear case of coloboma of the eye.

In regard to the vexed question of whether inflammation takes a share in causing some of the atypical colobomata of the choroid, reference should be made to a case published by Coats [8] in 1911, in which there were abnormalities in the choroid and retina in the temporal part of the equator and periphery of an eye showing coloboma of iris and lens at the corresponding part of the circle. The fundus appearances, as described by Coats, recall those in some of the cases in the present pedigree, and had there been no coloboma of the iris many observers would certainly have put them down to pre-natal inflammation. Coats gives reasons for believing that the abnormalities at the fundus in his case were due to early fœtal variation in the development of the periphery of the vitreous. If a similar explanation may hold for such cases as our V, 10, 11, 15, and 20 the conditions, on that hypothesis, would have to be considered as entirely developmental instead of partly inflammatory in origin.

We have not been able to find out accurately for all the insane persons in this pedigree the age at which definite symptoms of mental failure began; it is noteworthy, however, that the two congenital defectives (V, 16 and 20) are the offspring of a father (IV, 13) who appears not to have been insane until about 30 years of age. But we learn more by ignoring the age at the known onset of insanity, and attending to the age at death of those who died insane at 66, 65, and 62 respectively (III, 9, 11, 12); one of the latter (III, 9), dying insane at

66, had two sons who died insane at 32 and 37 respectively (IV, 10, 13). One of these two sons (IV, 13), who died insane at 37, begot two children who have been mentally deficient from birth (V, 16 and 20); the other (IV, 10) had five children (V, 9-12a); four of these are living and not one of them is normal, all having eye-changes and defective sight and one being also an imbecile; the fifth died quite young and no particulars are known.

There is no satisfactory evidence of this earlier culmination or earlier incidence (anticipation or ante-dating) in the eye-disease itself, considered apart from the mental imperfections, in this pedigree. In several of the eyes marked as " blind " or "bad sight " there are persistent remains of fœtal structures as well as post-natal pathological changes, and this association can hardly be regarded as accidental. Such association of developmental arrest with subsequent disease can be neither established nor denied for the cases of blindness in the earlier generations, for just as in some members of Generation V the eye-changes now known to be present would not have been suspected unless carefully looked for, so it is possible that in the earlier cases (such as III, 9 and IV, 8 and 13) abnormalities of the same character would have been found in one eye or both had the subjects been examined in childhood; and in this connexion it is to be noticed that in several of those who eventually became blind, or practically so, of both eyes, we are told that one eye had been useless from birth. In fact it is only for Generations III and IV that we know the age at which the sight became so bad in both eyes as to cause incapacity. This was generally in young adult life, between 20 and 30, but in IV, 10, we know that both eyes must have failed quite early, for he was in a blind school by the time he was about 9. The occurrence of developmental bodily defects in this pedigree has not been limited to the eyes; a by no means exhaustive investigation has shown, in addition, a frequency of small stature, and the occurrence of such special conditions as undescended testicle (IV, 13) and in one of the girls (V, 15) delayed growth and sexual evolution; the congenital defects of mentality have been already mentioned.

The subject of anticipation in insanity has recently been dealt with fully and in detail by Mott,[1] and study of his work confirms our belief in the importance of this character, and the urgent need for the collection of data bearing on its occurrence in other diseases upon a larger scale, and with greater accuracy, than has, so far as we are aware, hitherto been attempted. Some such facts and opinions have been recorded in reference to glaucoma (Lawford [17]), senile and præsenile cataract and diabetes (Nettleship [21]), three diseases which appear to have no points in common.[1] Some other maladies probably also show the same phenomenon. A few new cases of anticipation in diabetes are given further on in the present paper.

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[1] Mott's statistical method in this connexion is criticized by Karl Pearson in *Nature*, vol. xc, p. 334 (November 21, 1912).

A superficial inspection of the pedigree chart (fig. 1) shows firstly that, as to a considerable number of the individuals, no particulars are known except sex, and not always even that; secondly, that all the known cases of definite mental defect and eye-disease have occurred in two stocks (D. and H.) unrelated to each other by blood; and thirdly that marriage between an affected (insane) man of one stock and an affected (insane and blind) woman of the other stock, in Generation III, she herself also having insane kinsfolk, has been followed by mental and ocular disease in many of their descendants in IV and V.

If the affected stocks in III, IV and V are inspected rather more closely it will be found that they yield about 65 individuals born alive and surviving more than one year, that of this total 8 (or 9 if we count IV, 12, whose mental state is doubtful) were, or are, insane, imbecile or idiotic without known affection of sight, 5 others insane and blind, and 8 others affected with the family eye changes, but no mental defect. Of the remaining 42 at least 16, say two-fifths, have been ordinary paupers for longer or shorter periods, leaving only about 25 who can be called normal. Even of these, 2 are known to be tuberculous, at least 3 others died before 8 years of age, and several are still children. There have been a number of infantile deaths and miscarriages, probably from 15 to 20 in all, but these are not counted in the 65. We thus find at least 40 of the 65 (24 diseased and 16 paupers), or nearly two-thirds, unsound in their mind, or their eyes, or so circumstanced as to need aid from public funds. We of course attach no importance to these precise numbers, but it is of great moment to notice that the morbid conditions we are specially concerned with in this genealogy have descended directly from parent to child in every instance, with the single exception of III, 13, a tuberculous father believed to have been mentally sound, who left a son (IV, 27) who is insane.[2]

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[1] We are told by Adami [1] of experimental work within the last few years the tendency of which is to show that the offspring of animals that have been subjected to a certain toxic substance may be more, not less, susceptible than their parents were to the same poison. Evidently such a condition, if its occurrence is confirmed, may give us the clue to clinical "anticipation."

[2] But, as already mentioned it is possible that this man's (IV, 27) disease is general paralysis of the insane, in which event it is probably due to syphilis (see description of case).

The fertility of the insane members who had children has been high, but several of the normal sibships have also been large, *e.g.*, II, 3-5; III, 16-23, and several in IV. Of those who became insane in III and IV, two (III, 6 and IV, 27) are known or believed to have had no issue; IV, 24, is a young man only lately married.

DESCRIPTION OF THE PEDIGREE (fig. 1).

I, 1, a Scottish stonemason, D——, and I, 2, his wife, who had eleven sons (II, 3, 4, 5) and no daughters. The eldest (II, 3) was born at Dumfries about 1812, the other ten at Northampton, whither the parents (I, 1 and 2) migrated. All the eleven grew up and nearly all married and had children. Most of them were stonemasons like their father (I, 1); the youngest, however, a ship's steward, was drowned at sea, whilst the eldest, II, 3, a carpenter, reported to have had one seeing eye only, married twice and had apparently only one child (III, 4, born 1848), of whom nothing is known. In July, 1862, II, 3, was in a London workhouse (no particulars). The second son, Eli (II, 4), born 1815, married II, 6, of whose mental condition nothing is known, but she lived to a good age; they had the four children (III, 5 to 8). II, 7, John H., 1815 to 1886, and — 8, his wife (born 1814, but no other information): neither of them was related to II, 3—5. II, 7, was a working furrier until he was at least 46; he died in Claybury Lunatic Asylum in 1886, aged about 71, having been insane for at least two years previously, and an inmate of a London workhouse for several years before that (from the age of 63); we do not know his condition between the ages of 46 and 63 (1861 to 1878). He had five children (III, 9 to 13).

III, 5 to 8, four children, all males, of II, 4 and 6. III, 5, George D., 1846 to 1907, inmate of Claybury Lunatic Asylum for nearly a year before he died there in January, 1907, of catarrhal dysentery, aged 61; he suffered from mania with delusions of persecution, and was later noisy, excited, with tremors and slurred speech; had been a harness maker and a steady but moderate drinker; married at 20, his wife (III, 9) being ten years older; they had the children IV, 8 to 14. III, 6, born 1848; at age of 30 was inmate of Colney Hatch Asylum for five months, with a first attack of mania, and is said to have emigrated to America with parents, II, 4 and 6, and two brothers, III, 7 and 8, after leaving the asylum (about 1877); nothing more is known about him. III, 7 and 8, no particulars, but believed by informant (IV, 8) to have been sane.

III, 9 to 13, five children of II, 7 and 8.

III, 9, Elizabeth Emily H., 1837 to 1903; died of lobar pneumonia, aged about 66, in Hampshire County Asylum, where she had been for about ten weeks demented, weak, restless and refusing food; was also quite blind, and the corneæ showed much opacity; *post-mortem*, pneumonia and fatty degeneration of the heart. Had previously been in three asylums, the first occasion being when she was 24 (1861). From the history given by her eldest son

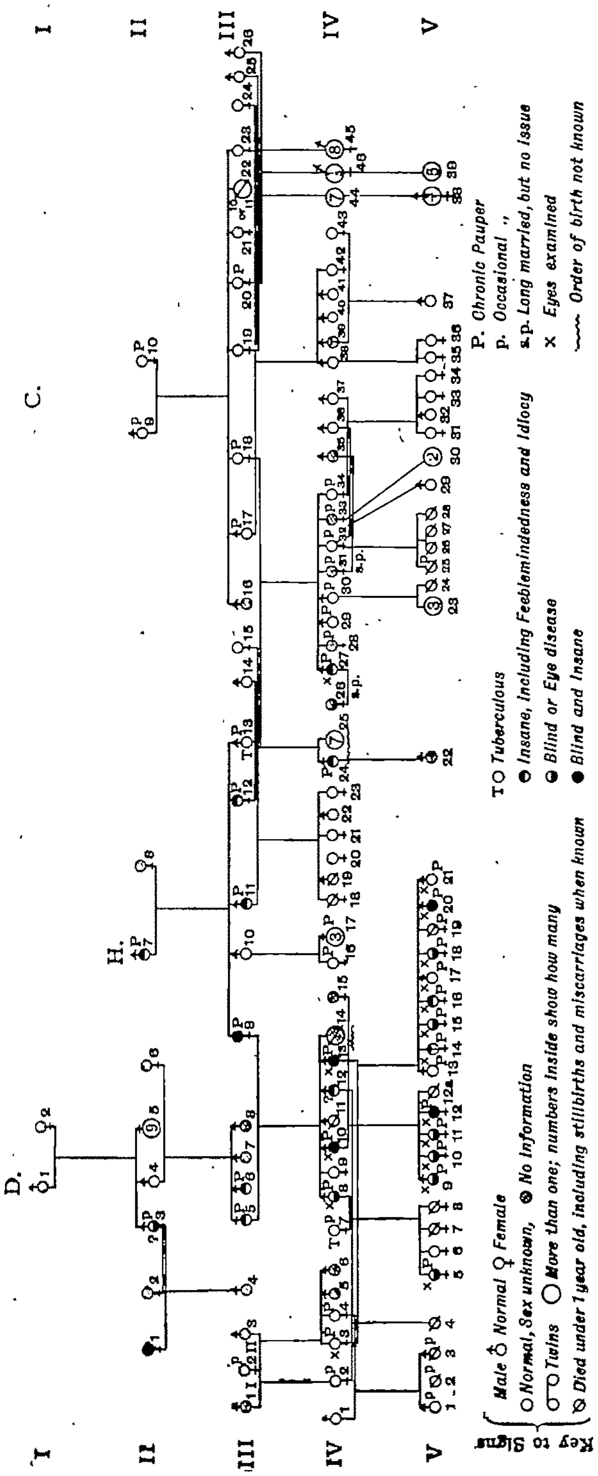
I
II
III
IV
V
D.
H.
C.
Key to Signs
Male ♂ Normal ♀ Female
○ Normal, Sex unknown, ⊗ No information
○○ Twins ◯ More than one; numbers inside show how many
Ø Died under 1 year old, including stillbirths and miscarriages when known
T○ Tuberculous
◐ Insane, including Feeblemindedness and Idiocy
◑ Blind or Eye disease
● Blind and Insane
P. Chronic Pauper
p. Occasional „
s.p. Long married, but no issue
× Eyes examined
〰 Order of birth not known

FIG. 1.—Insanity and complicated eye disease.

(IV, 8), she seems to have gone blind rather gradually about age 28 to 30 (*i.e.*, after her first attack of insanity), and we know she was 30 when she married III, 5, in 1867. Her eyes are said to have been operated upon at Moorfields Hospital when she was about 40 (say 1875), but her name cannot be found in the records of that period; the nature of her eye-disease therefore remains doubtful, but detachment of the retina is not excluded. She had five living children and several miscarriages (IV, 8 to 14).

III, 10, George H., born 1842, fell downstairs and broke his neck (between 1880 and 1885); was a heavy drinker, was married and had three sons and one or two daughters whom it has not been possible to trace (IV, 16 and 17).

III, 11 (William H., born 1844). His wife, III, 15—now (September, 1912) in a workhouse infirmary for the last eighteen months—states that he (III, 11) was in Colney Hatch for two years, about 1878 (age about 34), and in other asylums in 1888-90 and 1902-04, and died "mad with dropsy" in an infirmary in 1909, aged about 65. They had six children (IV, 18 to 23), of whom 18, born 1878, died at about one year; and 19, born 1886, at 6 months; 20, born 1880; 22, born 1882; and 21, born 1884, are unmarried. 23, born 1889, married recently (1912); no children yet.

III, 12.—Harriet, born about 1850 and married III, 14, a year her junior, about 1873; in 1874-75 was in Colney Hatch four months for first attack of puerperal insanity; discharged cured. Died July, 1912, aged about 62, of "paralysis of brain" (daughter's statement), not having been again in any asylum. Had large family, of whom eight (IV, 24 and 25) lived to grow up; seven of these were apparently normal in mind and eyes; but one (IV, 24), boy born about 1883, was insane about ten years ago (aged probably about 20), and in two asylums; recovered, and has since married and has a son (V, 22).

III, 13.—John, born about 1853, married III, 18, about 1870, she being a year or two older than he; they had eight children (IV, 27 to 34); he (III, 13) died of phthisis in a workhouse infirmary in 1910, aged about 57, having drifted apart from his wife for the last fourteen years of his life. Wife (III, 18) still living (1912), is a steady drinker. This couple, and all their children, have spent a large part of their time since 1883 in London workhouses, workhouse schools, or Poor Law infirmaries.

II, 9.—John C., 1815-1877, was in a workhouse for only two months before he died; his wife (II, 10) born 1826, still living (1912), has had parish relief for the last sixteen years. They (II, 9 and 10) had seven children who lived, and ten or eleven that died in infancy; neither these nor their descendants in IV and V call for special remark, except III, 16, who died at 40, cause unknown, and III, 20, who died of Bright's disease. Several have been paupers, and one (IV, 39) is said to be tuberculous. III, 19, separated from husband for years under magisterial order. III, 23, died of cancer several years ago.

III, 2 (1848-1902), concerns us only as being the mother of the wives of IV, 12 and 13. She (III, 2) married twice; her second family, of four, were born between 1876 and 1890; no particulars are known of her husbands; she herself had chronic Bright's disease, and died of intracranial hæmorrhage attributed to a fall from a seat in a public-house, the fall being put down to a fit; was said to have had "fits" before. Her eldest daughter (IV, 2) married IV, 12, and had one child that died in infancy. Another daughter (IV, 3), born 1876, married IV, 13, and had the nine children, V, 13-21 (see below).

IV, 8-14, issue of III, 5 and 9; six lived, and several miscarriages. IV, 8, George D., born 1865—*i.e.*, about a year before his mother married—possibly not a son of III, 5; this point is of interest because IV, 8, although he has the family eye-disease, is now, and has always been, mentally sound. He married at 22, wife (IV, 7) being 30, and a widow with three children; he had four children by her (V, 5-8); she (IV, 7) died, aged 45, in 1903, of phthisis (certificate seen). Condition of IV, 8, when seen, March, 1912, aged 47. Fairly intelligent, small stature, about 5 ft. 3 in., quite blind, umbrella mender, but has outdoor relief. Says R. eye "never any good, born with no sight." L. had good vision till he was about 22 (about when he married); in 1889, aged, say, 24, had advice at Moorfields Hospital, and went again in 1897, when he was told that the "retina" in this eye was "detached" (notes not obtainable), and subsequently lost all sight in it. Now R., tension normal, anterior chamber, rather deep, iris dirty brown, fine texture, adherent to remains of opaque lens, perception of light; L., tension normal, iris tremulous, no synechiæ, but acts incompletely to mydriatic, lens very cloudy at nucleus, but clear enough at periphery to transmit dull red reflex, which is consistent with transparent detachment of retina, apparently no perception of light. IV, 9, Charlotte, born 1868, died 1876, "bronchitis and congestion of lungs"; said to have seen well. IV, 10, William, 1869-1901, said to have had both eyes operated on when four years old by Mr. Bäder at Guy's Hospital, but his name cannot be found in the records at the corresponding period. It is certain that when about 9 he went into a school for the blind and learnt music; married and had four children (V, 9-12), the eldest being born about 1893. On August 30, 1901, IV, 10, was admitted to Hampshire County Asylum very weak and ill—sordes on lips, refused food, acute mania, quite blind, but no examination of eyes possible; died of exhaustion a fortnight later aged 32; said to have been a heavy drinker. His wife (IV, 15) deserted her children about 1903, and has not been heard of since. IV, 11, John, born 1870, died 1873; no details. IV, 12, Edward, born 1872; still living, said to be carman with good sight, but stated by step-sister (IV, 3) to be at times very excitable and violent, and threatening violence to himself and others, his wife (IV, 2) "going in fear of him." IV, 13, Henry, 1873-1910, married at 20 (1893), wife (IV, 3) being 17, and had nine children (V, 13-21) in thirteen years, first child, V, 13, being born seven and a half months after marriage. He (IV, 13) was "short-sighted," but saw quite well with L. eye till he was 24 (1897), when it failed rapidly in one day whilst at work; R. said to have been defective as long as he could remember. At St. Bartholomew's Hospital a few days after failure of L. (good) eye, the late Mr. Bowater Vernon found extensive detachment of retina in both eyes of more recent appearance in L. than R.; vision of R. (older detachment) being fingers, that of L. only perception of light.

L. underwent scleral puncture without benefit; gradually lost the remaining sight in both eyes, but (according to widow) continued sane and sober for some years. Then had delusions of suspicion with suicidal tendencies, took to alcohol, but could never carry much drink; and eventually became quite insane. In March, 1908, admitted at Bexley Asylum and died there two and half years later (November 17, 1910) aged 37; delusions of persecution, and later of exaltation—impulsive, noisy; and abusive; height 5ft. $\frac{1}{2}$in., L. testicle undescended, urine normal; blind of both eyes, R. lens densely opaque, L. radiating opacities in lens, upward coloboma from iridectomy and some vessels visible through edge of lens, optic disc not seen. In January, 1910, acute glaucomatous attack in R. permanently relieved by iridectomy; in April and June some irregular fever and phthisis seems to have been suspected, but symptoms passed off; November 16, acute pneumonia, T. 104°; 17th, died. His wife, IV, 3, seen June, 1912, aged 36, dark brown hair, brown irides, fundus dark and normal in each eye, vision of each $\frac{6}{6}$, and 1 J. easily, emmetropic refraction; intelligent woman: she and her husband were not blood relations. IV, 14, several miscarriages, the order of their occurrence not ascertained; nothing except the miscarriages pointing to syphilis in IV, 13, IV, 3, or their children.

IV, 27-34, issue of III, 13-18.

IV, 27, born 1873, now (1912) 39, said to be married to IV, 26, but they have no children; has been in prison over a dozen times for thieving during several years past. In March, 1912, admitted to Long Grove Asylum, Epsom; at first depressed and apprehensive, then, after a period of violent excitement, became maniacal, being excitable, garrulous, restless and extremely self-satisfied, with fantastic and disconnected delusions, and has had an attack suggestive of a general paralytic "seizure"; tendon jerks exaggerated, pupils normal when admitted. Syphilis denied and no physical evidence of it, but Wassermann reaction in blood and cerebro-spinal fluid positive. Eyes examined September 12, 1912 [E.N.]: fundus normal in all parts of each, R. myopia, about 1·5D.; L. emmetropia or slight hypermetropic, irides brown, choroids dark (hair black). Case thought to be probably general paralysis of the insane. Of the others in this sibship, born between 1874 and 1884, all have had Poor Law relief of one kind or another; IV, 29, has advanced heart disease; IV, 32, had by various men four illegitimate children (V, 25-28), including twins; all died at or soon after birth; she then married IV, 36, and by him has had one child that survives. IV, 34, married a man, IV, 37, who attempted suicide in 1911 because "he and his wife and family were destitute."

V, 5-8, four children of VI, 7 and 8.

V, 5, Elizabeth Emily D., born November, 1890, aged 22 when seen by E. N., April, 1912; black hair, fairly grown, intelligent, no illness during her several years' residence in blind school, no signs whatever of congenital syphilis. Could never see with L. eye, but as a child could see enough with R. to learn large letters. When about 13, R. got worse, and father was told at Moorfields Hospital that she had "something broken or detached" in the eye; operation advised but father refused it. Now (April, 1912) R. iris brown, acts fairly to homatropin, no synechiæ, tension normal, cornea, anterior chamber and lens normal; deep, opaque, white detachment of lower-outer part of retina, dullish red reflex in other parts, ? from shallow retinal detachment and diffuse haze of vitreous, retinal vessels not being well seen; optic disc normal, refraction (shadow test) somewhat, but not highly, myopic over red part of fundus; sees light but not fingers. L. rather shrunken, soft, no perception of light, opacity of lower part of cornea continuous with sclerotic, and iris adherent to this part but no sign of wound; pupil small and undilatable; dense, white, freely moving opacity deep behind iris (? lens or detached retina), no red reflex. V, 6, Harriet, born 1894, now 18, said to have good sight, in service, not seen. V, 7, Esther Sarah, born 1895, died aged about two months. V, 8, Rebecca, born 1897, died probably under 1 year.

V, 9-12a, five children of IV, 10 and 15.

V, 9, William D., born about 1893, seen April, 1912 [Mr. W. S. Inman and E. N.], aged 19, in a blind school for seven years past. Undergrown but fairly intelligent and in good health; no signs whatever of congenital syphilis. Began to attend school when 5 years old, and could see writing on black board at proper distance till about 8, then sight got so that he had to stand in front of class to see the writing, and soon afterwards was excused attending school. History of blow on R. by stone about this period. When 11 was taken to Moorfields Hospital, where R. eye was excised (January 4, 1904), and was noted as shrunken with transverse band on cornea, deep anterior chamber, occluded pupil, tension −, calcareous lens, bony choroid, retina represented by a mass of yellowish tissue. At same date, L. V. $\frac{8}{60}$, nystagmus, opacities in vitreous. Now (April, 1912), nystagmus, cornea and anterior chamber normal, iris brownish, acting well to mydriatic, but showing a slender thread of unpigmented pupillary membrane, passing from front quite across the pupil and attached to front of iris at each end; no pigment on lens-capsule, many freely moving threads and one large opacity in anterior part of vitreous; optic disc good colour but edge rather blurred, some tissue (? remains of hyaloid artery) on lower part, a narrow crescent on temporal side, retinal vessels normal; yellow spot fairly seen and looks normal, a patch of choroidal atrophy at inner and another at outer periphery; refraction near optic disc by estimation and shadows, hypermetropia about 2D., sees $\frac{4}{60}$ to $\frac{6}{60}$, better with +2D., and reads words of 8 J very close. In this case the bad sight of L. is probably due to incomplete development, whilst in R., perhaps originally the better eye, destructive changes were started by a comparatively slight contusion. V. 10, Constance: August, 1904, at Moorfields Hospital, Mr. W. T. Lister found R. divergent, opacity in vitreous attached to posterior lens-capsule, probably hyaloid artery, and fibrous bands in front of optic disc, refraction hypermetropic 5D.; L. no note of fundus, refraction hypermetropic 5D.; +3.5D., spectacles ordered for constant wear. She was then aged 6. December 16, 1908, aged 9, Mr. Parsons found substantially similar conditions in R., the cord in vitreous being regarded as remains of hyaloid artery; he also noted radiating fibrous bands passing outwards from temporal side of optic disc, hypermetropia

4·5D., with +3D. sees $\frac{6}{18}$; L. coarse opacities in vitreous, fibrous tissue near optic disc, with +3D. sees $\frac{6}{2}$. October 18, 1912, aged 14, seen by E. N. at Crondall District Schools, Hants. Wears her spectacles; is known to see badly; is dull in intellect but not badly defective, is in Fourth Standard; fairly grown and well developed physically, has menstruated regularly lately; hair brown and curly, irides blue-grey; all incisor teeth large and particularly well shaped; no suspicion of congenital syphilis in complexion or features. Rapid double lateral nystagmus of rather small range; keeps her head rotated to her R. and depressed towards L. shoulder, and keeps eyelids screwed up; pupils wide and round from mydriatic, no trace of pupillary membrane; R. a single, freely floating string in vitreous, which may be remains of hyaloid artery [I had not then seen the Moorfields notes.—E. N.]; lower part of retina from optic disc outwards to beyond yellow spot shows whitish haze, the haze ceasing above, a little below yellow spot, by a sharply defined horizontal line or edge; downwards the haze gradually ceases, and it is nowhere dense enough entirely to conceal the choroid; lower half of fundus, where retinal haze has ceased, shows extensive choroidal changes, in form of areas of incomplete atrophy without sharply cut borders, and some highly pigmented patches; there are also numerous scattered smaller pigment spots, which appear to lie in the retina. The general appearances suggest extensive, very shallow and nearly transparent detachment of lower half of retina, drawn tight at level of yellow spot; but I could not prove detachment by measurement, and the interpretation put upon the appearances at Moorfields in 1904 and 1908, congenital fibrous bands in front of optic disc and retina, may probably be correct. There is nothing to show when the existing choroido-retinal atrophy and pigment changes came on. L. similar hazy retina, simulating detachment in lower half, precisely symmetrical with that in R., but no choroidal patches or pigmentation, and no opacity seen in vitreous; pigment epithelium shows coarse stippling (? normal) in parts. Vision not tested. V, 11, Emma, says she is 9 now (October, 1912), and was entered as 8 when taken to Mr. Worth at Moorfields Hospital last February, but recorded as 5 when admitted at Crondall Schools on May 30, 1906. If the last entry was correct when made she must now be 11, or, allowing for months not counted, 10 at least. Seen at Crondall by E. N., October 18, 1912; growth normal for 9, but if 11 she is decidedly undergrown; sight very poor but makes up for it by quick receptiveness, good memory and good gift for arithmetic; in Second Standard (about right for 9 years old). Teeth very good, like V, 10; no suspicion of congenital syphilis in skin or features. Irides blue-grey, hair lightish brown with golden sheen. No nystagmus. Vision not tested. Pupils under mydriatic. R. eye pupil very little dilated, many posterior synechiæ and fine pigment on lens-capsule, no proof of pupillary membrane, lower half of iris slightly green as compared with L.; diffuse white haze of lens, no fundus reflex; no perception of light; eye not shrunk; no sign of wound and no history to be got; eye gives no trouble. On February 8 last (8 months) the lens was nearly or quite clear, and Mr. Worth, at Moorfields, recorded a grey reflex from deep in the globe with some fixed cholesterin crystals, posterior synechiæ as now, no keratitis punctata, no fundus details visible, tension normal. L. read $\frac{6}{6}$, with +1D. at Mr. Worth's examination, and the existing fundus change was not seen; at the October examination, I [E. N.] found fundus normal except at extreme ophthalmoscopic limit of temporal periphery, where is a large rounded patch of dense grey-white retina, apparently detached, and adjacent to its posterior border a round patch of pigmented and partially atrophied choroid smaller than the retinal area, the two together forming a figure of eight. V, 12, Mabel, sent from workhouse to Western Counties Asylum for Training the Feeble-minded at Starcross, on February 1, 1905, aged 6 (born September 11, 1899). In December, 1907, the Ophthalmic Consultant to the Asylum found in L. a "pearly reflex" from fundus, "probably detached retina," and refraction of R. hypermetropia at least 4D.; she kept eyelids closed and was difficult to examine. In May, 1910, the same gentleman found definite cataract in L., with posterior synechiæ, and in R. an irregular, bubbly-looking patch at posterior surface of lens, obviously dense enough to interfere with sight, refraction (shadow test) as before. Seen by E. N., with Dr. H. Maturin, at Winchfield Workhouse, October 28, 1912; had been sent back from Starcross in November, 1911, no further improvement in mentality being possible. Is now 13, a certified imbecile, fairly good tempered, can feed but not wash herself, habits cleanly, can say a few words indistinctly, smiles when pleased; all teeth of both jaws quite sound, incisors large and well shaped; walks well, can knit a little, fairly well grown (slightly undersized). Eyes difficult to examine; irregular horizontal nystagmus. R. pupil well dilated by mydriatic, iris blue-grey, cornea normal, much opacity at back of lens; irregularly reticulated, not radiating, and not specially dense at pole; no details of fundus could be got either by indirect or direct method, the opacity interfered considerably, and she always looked at the mirror; too unruly to allow careful examination by direct method. L. very white, conspicuous cataract, and old iritic adhesions, no evidence of wound; iris about same colour as R. (notes made before report had been sent from Starcross Asylum).

V, 13-21, nine children of IV, 3 and 13.

V, 13, Henry D., born August 10, 1894, seven and a half months after parents' marriage, but was supposed not to have been premature; seen [by E. N.] June, 1912, aged 17-18; no signs of congenital syphilis; does not resemble in features his brothers and sisters seen at same time (? was IV, 13, not his father?); brown hair, blue irides, V. $\frac{6}{6}$ each eye, slight hypermetropia, fundi normal; V, 14, Margaret, aged 15, born September 3, 1896; at work, and could not be seen; began glasses at age 11, and when 13 (January, 1911) was ordered at Moorfields Hospital R. − 0·5D. s., L. − 2D. s., — 1D. c, axis vertical, and with these saw $\frac{6}{6}$ with each eye. When about 12 was certified as having "Tubercular disease of knee-joint, lungs not affected." V, 15, Ethel, aged 14, born July 5, 1898, went to ordinary school before she was 8; when 8 or 9 was sent to Blind School, where Mr. Bishop Harman found much the same condition of fundus and V. in both eyes as now (1912). Seen [by E. N.] April, 1912, aged 14, bright, intelligent, healthy-looking, but both in stature and development like a child of 10; no signs of congenital syphilis; hair and irides full brown. Eyes show coarse, irregular nystagmus; R. pupil acts to light and dilates fairly to mydriatic, but shows several posterior synechiæ and a separate spot of pigment on lens-capsule; the synechiæ cause little distortion of pupil, one is unpigmented, and some of them start from front of iris, all pointing to iritis either before or very soon after birth; cornea, lens and vitreous normal, retinal vessels full size, and optic disc normal or rather hazy; no detachment of retina but at extreme periphery, chiefly downwards, very large areas of choroidal disease, some white, others somewhat but not extremely pigmented, their borders convex in large curves towards equator; V. $\frac{6}{6}$ barely, and words of 1 J. at 5 in., refraction (shadows) myopic about 3D. and 4·5D. and sight improved to $\frac{6}{36}$ with − 2D. s. − 1·5D. c., axis horizontal, but the cylinder hardly appreciated. L. only sees 18 J. close, no trace of iritis or pupillary membrane; cornea, iris, lens, vitreous, optic disc and neighbouring retinal vessels normal, but fundus shows abundant choroido-retinal changes: (*a*) peripheral areas of choroidal atrophy, (*b*) numerous coal-black pigment dots and spots which probably lie in the retina, but are not of bone-corpuscle shape, (*c*) a large area, narrow near optic disc, widening towards periphery downwards, of incompletely atrophied choroid over parts of which the retina appears streaky and hazy, or the appearance may denote a subretinal formation; no proof of detachment (*cf.* description of fundus in V, 10). The fundus changes not like those in congenital syphilis. V, 16, Lilian, born December, 1900; aged $12\frac{7}{12}$ when seen by E. N. with Dr. Sherlock at Tooting Idiot Asylum, June 21, 1912, where she had been for four months; head of ordinary size and shape; pupils acted to light, and dilated well to mydriatic; quite idiotic and state of vision cannot be gauged, but not considered to be blind, and during ophthalmoscopic examination nearly always looked at the mirror: full exploration of fundi impossible, but no disease could be made out; fundus reflex bright red, retinal vessels normal, and optic disc (seen in one eye only) looked normal; refraction (shadows) definitely myopic but degree not made out. Previous history: age 2 years, certified "rickets and hydrocephalus," about a year later "likely to grow up an idiot, cannot sit up or walk," and a few months later "water on brain." Has been in one asylum or another since age $7\frac{1}{2}$. V, 17, Edward, aged 10, born July, 1902, seen [E. N.] June, 1912, bright and intelligent; no signs of congenital syphilis in teeth or physiognomy; head well-shaped, hair dark brown, irides grey with pigmented inner circle; V, $\frac{6}{6}$ each eye, refraction slightly hypermetropic, fundi normal. V, 18, Elizabeth Emily, born October, 1904, now $7\frac{8}{12}$ (June, 1912). In March, 1909, aged about $4\frac{1}{2}$, Mr. F. A. C. Tyrrell at Brentwood School found myopia 4·5D. in R., and 3D. in L.; he made no ophthalmoscopic note, but obviously the condition now present in R., even if it had begun then, could not possibly at that time have assumed its present proportions. Seen June 14, 1912 [E. N]., aged $7\frac{8}{12}$, wearing spectacles − 3D. and reported as doing well at school; milk teeth very good, no permanent incisors up; hair dark brown, irides brown; constant lateral nystagmus, which mother did not notice till after a "fit" attributed to exposure to sun at age 2 years, no other fits; eyes (after mydriatic), R. deep, universal detachment of retina, hardly any red reflex; L. at extreme outer periphery a large very white patch composed partly of subretinal deposit, partly of exposed sclerotic; the retinal vessels easily seen on front of this patch by direct method without a lens, hence probably there is some detachment, rest of fundus normal; refraction at centre of fundus, myopia ·3D. (measured before Mr. Tyrrell's notes had been seen). V, 19, born September, 1905, died within an hour. V, 20, William, born August, 1906. Seen at Herne Bay with Dr. C. K. Bowes, July, 1912, aged 6; feeble minded but clean, good-tempered, stands and walks well, feeds himself with a spoon, and can speak a little; sight believed to be quite good, but is too silly to respond to any tests; head of ordinary size, larger behind than in front; hair dark brown. Eyes: irides brown and act well to mydriatic, corneæ normal, lenses show apparent haze of lamellar type with brighter peripheral ring, but no measurable lack of transparency, shadow test shows low degree of myopia at 4 ft., optic disc and retinal vessels normal in both, and no myopic changes; in L., at outer periphery, a large, grey-white area of detached retina with sharply defined, circular, posterior border; no changes found in R. though carefully looked for. Slight varying horizontal nystagmus in ordinary daylight increased in lateral positions: it disappeared under ophthalmoscopic examination. V, 21, Albert, born 1907, seen June, 1912, aged 5; history of rickets, thought to be backward; light brown hair, blue irides; alternating divergent squint; shadow test shows myopia not exceeding 1D. in R. and emmetropia in L.; media and fundus normal in each, and choroids fair.

PART II.—OTHER CASES OF ANTICIPATION IN SUCCESSIVE GENERATIONS.

The most recent published statements as to anticipation in diabetes and other maladies that I know of are by Pfaundler [31] and Friedel Pick [32]. Professor Pick has published the following pedigrees, and has kindly added some details by letter since publication.

In one of these (fig. 2), given to Pick [33] by Dr. C. von Noorden, and to be known as "Noorden's first case" the diabetes showed[1] at age 40 and 56 respectively in two members of Generation I; at age 37 in the diabetic of Generation II, and at age 23, 22 and 20 respectively in the three victims in Generation III.[2]

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[1] Letter from Professor Pick, August 21, 1912; the wording is plain: "das Lebensalter des Auftretens des Diabetes markiert."

[2] There is some confusion; these numbers are from the *Diagram* in the paper in *Deutsch. med. Wochenschr.*, 1911, No. 32. In Pick's remarks in the *Verhandl. d. Kongr.*, already referred to, the ages in what appears to be the same case are stated to be 60 to 70 for the *great*-grandparents, 50 to 60 for their children, 20 for their *great*-grandchildren.

In another (fig. 3) published in 1912, (Pick [34]) and to be known as "Noorden's second case," no ages are published, but Professor Pick has very kindly sent them to me by letter, and in this case he tells me they show the ages at *death*.

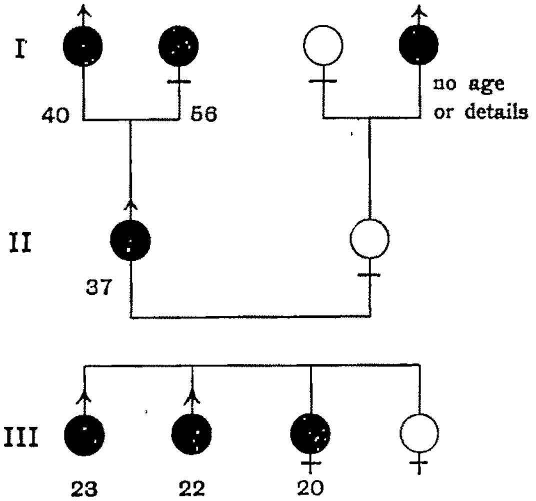

FIG. 2.—Anticipation in hereditary diabetes: numbers show ages at onset. (Von Noorden's first case.)

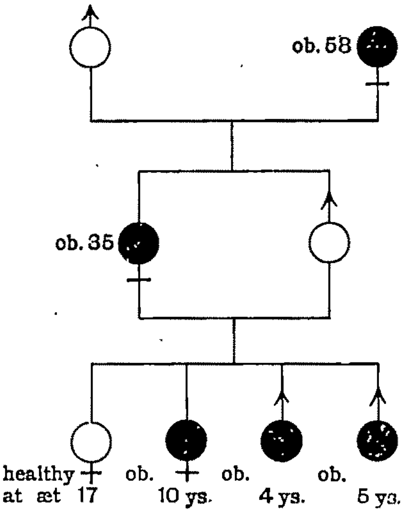

FIG. 3.—Anticipation in hereditary diabetes, showing ages at death. (Von Noorden's second case.)

In a third case (fig. 4) given to Pick by Dr. Přibram [35], although the exact ages are not stated, the context implies that the disease anticipated in generations.

Fig. 5 shows an unpublished pedigree begun by the writer and lately verified and much extended by Dr. C. H. Usher, of Aberdeen, and Dr. Alexander Wood, of Longside, Aberdeenshire.

In March, 1888 (P. 16, p. 19), I [E. N.], saw Mr. M. . . . aged 56, unmarried, with incomplete cataracts, chiefly nuclear, and rather more advanced in R.; fundus visible in each and showed no changes; adhesions in each from an attack of iritis without severe pain four years previously. Known to have been diabetic for some time, and now had dry skin, constipation, thirst and good but "not ravenous" appetite; breath of sweet odour; urine now 1040, much sugar. Said he had "all his life been thirsty." Ten years before (aged about 45) lost L. arm in a machine accident, immediate amputation, recovered well. I extracted the R. lens three months after preliminary iridectomy, he becoming fatter and his general condition better during the wait; but quiet plastic iritis with proliferation of uveal pigment followed the extraction and recurred after a second iridectomy and removal of membrane, and eventually the eye became rather soft and retained only perception of light limited to temporal part of field. L. eye not operated on. Lived to be 60; immediate cause of death, influenza; L. eye became much worse some time before he died. He is III, 19, in the Pedigree Chart fig. 5. He told me that several cases of diabetes had occurred on his father's side, but I made no further inquiries until the present year, when Mr. Usher and Dr. Alexander Wood have at much trouble obtained for me the data furnishing the figure. Twelve undoubted cases of diabetes have been discovered, including III, 19, above described. Only three of these had children. II, 2, who died of diabetes at 56 (in 1854), had a

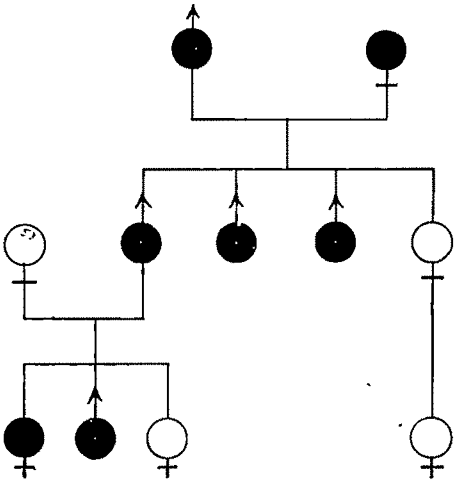

FIG. 4.—Hereditary diabetes: anticipation implied. (Přibram's case.)

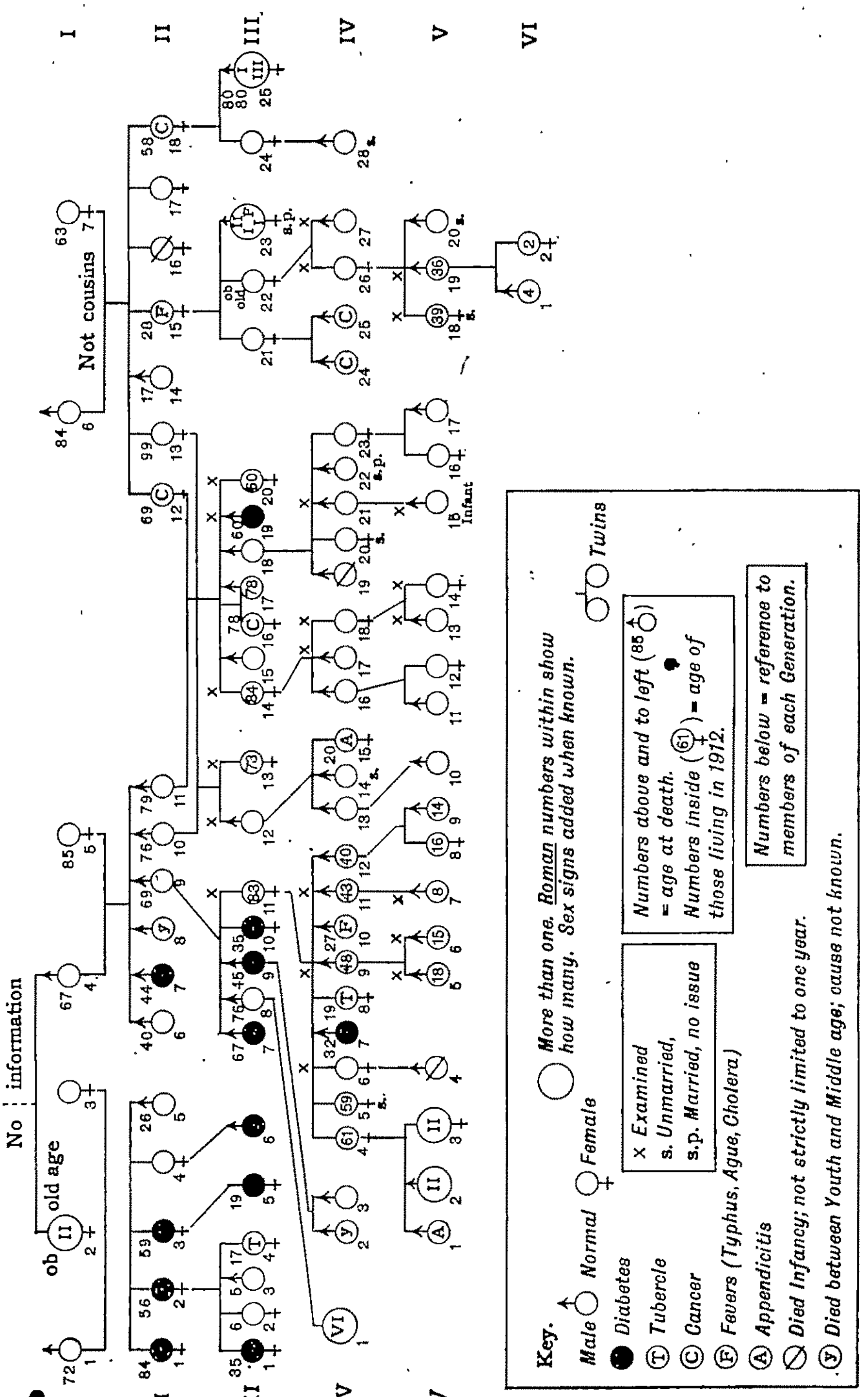
Key.
Male Normal Female
Diabetes
Tubercle
Cancer
Fevers (Typhus, Ague, Cholera)
Appendicitis
Died Infancy; not strictly limited to one year.
Died between Youth and Middle age; cause not known.
× Examined
s. Unmarried,
s.p. Married, no issue
More than one. Roman numbers within show how many. Sex signs added when known.
Twins
Numbers above and to left (85) = age at death.
Numbers inside (61) = age of those living in 1912.
Numbers below = reference to members of each Generation.
No information
old age
Not cousins
I
II
III
IV
V
VI

FIG. 5.—Family diabetes showing anticipation in some of the cases.

daughter III, 1, who died of diabetes at 35 (1870) unmarried. II, 3, who died of diabetes at 59 (1860), had an illegitimate daughter, III, 5, who died of diabetes at 19 in 1840, twenty years before her mother. In both these, therefore, anticipation was well marked. III, 9, who died of diabetes at 45, had only two children, IV, 2 and 3; the former died unexpectedly of "heart disease, duration one day" at 14 (1891), after a long and debilitating illness which may have been diabetes, or perhaps tubercle; no particulars known of the other child (IV, 3). None of the other diabetics married. The average age at death of the four diabetics in II was 61 (range 44 to 84), that of the six in III was 43½ (range 19 to 67; age unknown in III, 6); and the single known case in IV died at 32. The cause of and age at death of II, 4, not known, nor do we know the age at death of her diabetic son (III, 6).

III, 2, died at 6; III, 3, at 5, causes unknown; III, 4, at 17, tuberculous; so that not one of the issue of the diabetic II, 2, left offspring. IV, 8, sister of the diabetic IV, 7, died at 19, of phthisis. II, 9, father of three diabetics, died at 69, of delirium tremens. The normals, II, 10 and 11, and III, 11, all with diabetic brothers or sisters, have left numerous descendants in III, IV and V, with only two known diabetics. At least five cases of cancer are recorded in the non-diabetic division of the pedigree, viz.: II, 12 and 18; III, 16; IV, 24 and 25. There appear to have been but few infantile deaths. Of III, quite five are living; III, 11, aged 83; III, 13, aged 73; III, 14, aged 84; III, 17, aged 78; III, 20, aged about 60, and several lived to over 80; and much the same is true in Generations I and II. No cases of tubercle are mentioned in the non-diabetic half of the pedigree. A few of course died of fevers, acute illness or accident, and a few have been lost sight of. No neuroses of any kind are mentioned. The pedigree as it stands appears to show that the descent of hereditary diabetes, although usually continuous, may occasionally be interrupted; for, although we cannot assert that II, 11 (father of III, 19) was free, I am assured that III, 11 (mother of IV, 7), still living aged 83, is so. [E. N.]

PART III.—CASES MORE OR LESS COMPARABLE WITH THE SERIES IN PART I. [fig. 1].

Although I do not know of any series of cases of family choroidal disease leading to detachment of the retina such as those shown in fig. 1, certain groups must be mentioned some at least of which may be allied to them.

CASES OF EXTENSIVE COARSE DISORGANIZATION OF CHOROID IN INFANTS, OFTEN ASSOCIATED WITH MENTAL DEFECT.

In some of the following cases arrest of development of the central area of the choroid ("macular coloboma") may have occurred along with choroiditis, but none of them appear to the writer to have been only coloboma.

CASE 1.—*Extensive Choroidal Atrophy in an Infant.*

Female, seen at age 9 months, and again at 5 years 3 months. Eyes looked small, nystagmus, convergent squint, refraction probably myopia, at 9 months. At 5 years 3 months, could see by holding very close; fundi same in both eyes, very large patches of complete choroidal atrophy mostly at central region and to temporal side of optic disc, with much pigment running on to them like iritic adhesions; discs rather hazy, retinal vessels normal. No syphilis; no family history of bad sight; patient second of four, sexes not given; No. 1 living, reported normal; No. 2 patient; Nos. 3 and 4 ob. 1 year 6 months, diarrhœa. Mentality not noted but presumably good. (Hutchinson [13].)

CASE 2.—*Extreme Choroido-retinal Disease in an Infant whose Cranium, at first too small, became afterwards hydrocephalic.*

Female, 3 months (1875) has never taken notice, pupils act to light and dilate to mydriatic: well nourished; cranium small, and face smaller? on L. side; in both eyes many large areas of complete choroidal atrophy, some intensely pigmented, others free from pigment; at region of optic disc these patches more or less concealed by dense white opacity of retina many times larger than, and entirely concealing, discs and retinal vessels; retinal vessels beyond opaque area normal. When seen several months later, still seemed quite blind, and head had slowly enlarged to well-marked hydrocephalus. Patient third born, mother ill, vomiting and constipation, when four and a half months pregnant with her; first born, seen at age 4 years, no signs of syphilis; second, aged 2, not seen, sex not noted. (Nettleship [22].)

CASE 3.—*Central Choroidal Atrophy in Microcephalic Idiot.*

Male, 12 months, 1880; takes no notice, but pupils act fairly to light, cranium small, ridging and premature closure of sutures, weak in back, no use in legs (no rickets), "will doubtless be idiotic"; large area of superficial atrophy of choroid at macular region in R., and of complete atrophy (white sclerotic with pigmented border and tortuous emergent vessels at centre), position not noted, in L; is fourth born. First had large head and ob. "convulsions," age and sex not noted; Nos. 2 and 3 living: presumably normal, sex not noted. (Nettleship [23].)

CASE 4.—*Abundant Choroiditis in Infant with Premature Closure of Sutures. Tubercle in Siblings.*

Female, 10 months (1883), has never taken notice, but pupils act; was well till 5 months, then refused breast and has grown very little since: premature closure of sutures; in both eyes large patches of choroidal atrophy, a few complete but mostly of inner layer only, no exudation or new tissue, retinal vessels normal; R. disc very hazy; L. disc normal. No history or evidence of syphilis. Patient third of three; Nos. 1 and 2 (sexes not noted) both ob. aged 3 years, one of "consumption," the other apparently of tubercular meningitis. (Nettleship [24].)

CASE 5.—*Coloboma of Iris in one eye, extensive Choroiditis in both, probably Mental Defect.*

Infant, 9 months, sex not recorded (1879); sutures closed, numerous fits since 2 months; L. eye too small, coloboma of iris downwards, very large and highly pigmented patches of atrophied choroid, but "no coloboma seen"; R. doubtful perception of light, many small patches (none so large as optic disc) of pinkish choroiditis, like "deep deposit beneath denuded epithelium," none of them pigmented; optic disc normal, eye normal size, no note as to activity of pupil. No notes of family history. (Nettleship [25].)

W. T. Lister [18] has recorded a "Case of Macular Coloboma associated with Old Choroiditis," with a plate showing the ophthalmoscopic appearances in both eyes of a lad of 19, whose sight had always been in its then condition. The patient was the youngest of four children, was a very delicate baby, had whooping-cough at 3 months, then rickets; had no fits; no history or signs of congenital or of acquired syphilis, and no family history of tubercle. Marshall [19] published a case of extensive coloboma of choroid and iris in both eyes, in which inflammatory complications occurred in one eye. Cosmetatos [7] has also published a case of coloboma of the macula with some separate patches of choroiditis in an otherwise healthy child. Reference must also be made to cases of coarse macular disease believed to have had tubercular origin recorded by Mr. Harrison Butler [6]; of these Case 4 showed signs of pre-natal iritis and general arrest in the R. eye, and in the L. a large patch of choroidal atrophy at the macula.

The following five cases have not been published before:—

CASE 6.—*Gross Choroidal Disease in an Idiot.*

Male, aged 7 or 8 years, seen at National Hospital, Queen Square, April 1882 (P. 6, p. 133); in for recent paralysis of R. hand with athetoid movements; idiotic, undergrown and looks only aged 4, cranium small, is not blind. In both eyes very large patches of choroidal atrophy, mostly quite white or greyish-white without much pigmentation, some incompletely atrophic; more in L. than R.; not coloboma, though one patch in L. is in lower part; not like ordinary syphilitic choroiditis. No note as to family history.

CASE 7.—*Gross Choroidal Disease in Idiotic Infant.*

Male, aged 7 months, issue of first pregnancy, parents' ages not given. Takes little notice, but pupils act to light; R. several large patches of pigmented choroidal atrophy, optic disc not well seen; L. single immense area of complete choroidal atrophy with much pigmentation, optic disc pale; anterior fontanelle much too small, front of head small, nose large, ? idiotic; had thrush, but nothing else pointing to syphilis. Seen again aged 1 year 6 months, and appeared to see pretty well, but "cannot stand yet." Family history not taken,

CASE 8.—*Gross Choroidal Disease with Craniotabes and early closure of Fontanelle. Small Head.*

Male, aged 7 months, 1894 (M. O.P. iii, p. 150), always been thin and delicate, no syphilitic history; head rather small, soft places in occipital region; two months later anterior fontanelle nearly closed but sutures not ridged. In each eye an enormous circular area of sharply defined choroidal atrophy with much pigmentation but no grey tissue, larger in R. than L.; situation not stated, but as optic discs were blue-grey the choroidal disease was probably central and may have been macular coloboma altered by inflammatory change; retinal vessels normal; pupils act to light. Seen again aged about 3 years 6 months, strong, active, irritable, head small, pupils act to light, fundi as before, seems to see light. Patient youngest of six. No. 1, female, born about four and a half years before patient, seen aged 5 years, rickety bone-ends and forehead, good milk teeth, no signs of syphilis, no note of eyes. (2) Miscarriage. (3) Female, born two years after first, seen aged 3 years, no signs of syphilis, no note of eyes. (4) Miscarriage. (5) ? Sex, born eighth month, ob. five weeks. (6) Patient. No other family history recorded.

CASE 9.—*Gross Choroidal Exudation and Atrophy with History of Illness, probably Meningitis, in Infancy. Small Cranium, keeled sagittal suture. Defect of Hand.*

Male (P. 40, p. 169), when aged a few months, had an illness thought to be meningitis, but opinions differed; sight never been better than when I saw him aged 17 years. Aged 17 (1896), very large area of peripapillary deposit in each eye, and a large patch of choroidal atrophy to nasal side of it in one eye, posterior polar opacities in each lens, and slight opacities in each vitreous; the retino-choroidal deposit area shows well-defined curved borders, not fibrous like opaque nerve-fibres, and is crossed by many vessels, some traceable to optic discs, others lost in the white; R. optic disc difficult to see, L. clearer; eyes look small, cornea 8-9 mm. only, but refraction (shadow test) myopia 13D. in each, with some astigmatism in R. V. corrected = fingers at 2 m. and reads 10 J with magnifier at one inch; irides blue-grey, pupils very active; hair dark, cranium small, sagittal suture keeled, ears projecting, teeth large and good, good memory, quite intelligent, and manages to read a good deal. Aged 23, now general opalescence of both lenses with "white china" patch in anterior cortex of R. Is first born of six, the other five normal. Family history not asked.

CASE 10.—*Choroidal Disease, Detachment of Retina and perhaps Remains of Hyaloid Artery in one Eye of otherwise Normal Infant.*

Male (P. 49, p. 10), born full time, without instruments, good health, no illness. Squint of R. noticed at six months. Eyes not examined till 1 year 8 months when (January, 1899) L. fundus found quite normal; in R., which was now divergent and decidedly smaller than L., but with tension normal and pupil acting only consensually with L., there was a large, deep detachment of outer half of retina with what looked like a translucent cyst at extreme anterior part and one or two opaque patches (to focal examination), and a very large area of choroidal atrophy far back near the posterior part of the detachment, also a cord varying in thickness like a string of sausages in the vitreous, possibly remains of hyaloid artery. No history or evidence of syphilis, no known tubercle. Patient is third born of four. (1) Male, aged 7, 1899, normal. (2) Male, died at birth, difficult instrumental delivery, two years after first. (3) Patient, born five and a half years after first. (4) Female, born eleven months after third, normal at age 9 months.

CASE 11.—*Extensive Choroidal Atrophy with Myopia from Birth or Early Life, Recent Loss of One Eye by Irido-choroiditis. Defective Intelligence. Meningocele. Family History of Bad Sight and Epilepsy.*

Male, aged 30, 1892 (P. 25, p. 5), "only three-quarters intelligent," very long, narrow head, prominent forehead, occipital meningocele as large as a Tangerine orange; never any fits or paralysis. Sight seems never to have been better than now. R. could see light till a year ago, now no perception of light, lens opaque, iritic adhesions; L. sees 15 or 16 J., cornea, iris, pupil, lens, vitreous normal, refraction myopia about 10D. (ophthalmoscopic measurement only and probably estimated too high), very large areas of complete choroidal atrophy, very little pigmented, optic disc enclosed in one such and is nearly as white as the exposed sclerotic. He is ninth born of twelve, all but two living, as follows (ages as in 1892):—

(1) Ob. a few weeks, sex not stated. (2) Female, aged 44, "short sight," and wears glasses, but does not see really well, and has had advice. (3) Male, aged 42, same as No. 2 in all respects. (4) Male, aged 40, good sight. (5) Female, aged 38, good sight. (6) Male, aged 36, "quite blind," is a minister. (7) Male, ob. aged 27, would be between 32 and 36 if alive; "short-sighted," and wore glasses, but did not see very well (as Nos. 2 and 3). (8) Female, aged 32, epileptic, blind of one eye, and sees badly with other. (9) Male, aged 30, patient; (10) Male, aged 28; (11) Female, aged 26; (12) Male, aged 24—all reported as normal, and having good sight. No consanguinity of ancestors (all four grandparents known), and no family history of bad sight or neuroses obtained at preliminary inquiry.

Other examples of family disease of some part of the nervous system associated with severe choroido-retinal changes in early life are known, apart of course from the ordinary form of retinitis pigmentosa, and its frequently associated deafness and mental defect. One such case was unwittingly published as two separate cases at widely different dates, first by the late Mr. Zachariah Laurence, and then by Sir Jonathan Hutchinson. The two accounts supplement each other. The essential features were as follows;—

CASE 12.—A sibship of ten, nine males and one, the tenth born, female, of whom only one died (male, of smallpox at 6 weeks of age). Three of the males (third, fourth and sixth born), and the female (tenth born) suffered from progressive failure of sight and progressive paraplegia with dulness of intellect, arrested development of sexual system and some of them from arrested bodily growth. The fundi showed very extensive incomplete atrophy of choroid, mainly at the central area, with some atypical pigment spots in the retina, and hypermetropic refraction. The failure both of sight and leg-power began in childhood, except that in the girl the leg-weakness did not set in until she was nearly 18. One of the affected boys became insane. The two eldest were fine men, married and had children. The family history, carefully inquired into, threw no light on the cause of the affection.[1]

I have less detailed notes of the followed unpublished cases, which for the present may be grouped with the last.

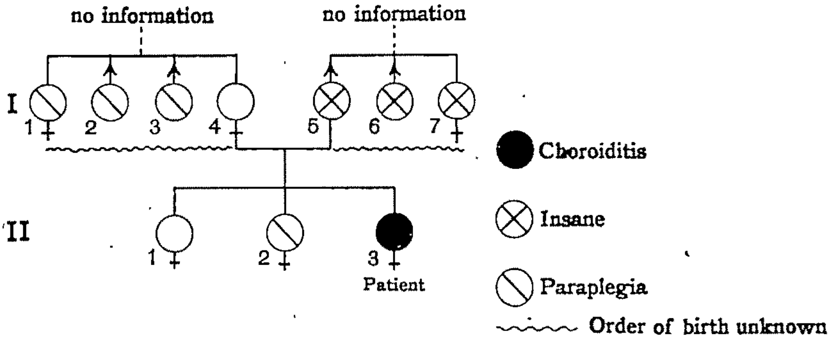

FIG. 6.—Pedigree showing choroiditis, insanity and paraplegia.

CASE 13.—*Excessive old Choroiditis of "Island" Type. Family History of Insanity.*

Female, aged 29, 1894 (fig. 6, II, 3) (P. 30, 238): no eye disease except the choroiditis, all of which looks old, though history of recent worsening of V. in R. may point to one or more comparatively new exudations. R. V. not $\frac{6}{60}$; said to have failed six months ago; L., $\frac{6}{9}$, considered as quite good. Fundus changes more extensive, but not looking more recent, in R. than in L.: very abundant black islands of choroiditis, each with a narrow pale border, and some showing fibrous tissue, yellow spot involved in R., not involved in L.; discs and retinal vessels normal. Emotional, subject to bronchitis, and was always delicate (report from her doctor); upper incisors absent, "broke off short." Family history supplied by the medical attendant. As no mention is made of consanguinity between 4 and 5 in Generation I, I assume them to be from unrelated stocks.

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[1] Zachariah Laurence [16], Hutchinson [14A], with coloured ophthalmoscopic plate showing condition of fundus in one of the cases about 1878. The two narratives combined and summarized by Nettleship [25A].

I, 4, patient's mother, normal, active and intelligent to date of writing (1894). I, 1, 2, 3, siblings of I, 4; I, 1, ob. paraplegia from "softening of spinal cord"; I, 2, alive, but has advancing paraplegia (1894); I, 3, ob., aged 71, softening of brain and paraplegia. I, 5, patient's father, hypochondriac and chronically dyspeptic. I, 6 and 7, siblings of I, 5; I, 6, ob. in a lunatic asylum; I, 7, ob. insane at home. II, 1, 2, 3, issue of I, 4 and 5; there were no other births. II, 1, aged 36, fairly healthy to date, except two attacks of acute rheumatism lasting three and six weeks respectively. II, 2, ob., aged 25, with paraplegia of quite three years' duration, due to "softening of the cord," actual cause of death, acute tuberculosis. II, 3, patient.

CASE 14.—*Gross Choroidal Disease in One Eye. Insanity in near Relations.*

Female, aged 36, 1876 (Nettleship [26]). L. eye, a single, very large, oblong patch of old choroiditis almost covered by coal-black pigment situated below and to nasal side of optic disc, media clear; V. $\frac{6}{18}$, not improvable; R. eye normal. No syphilis. Is seventh of eight, as follows (ages as in 1876): (1) Male, was an idiot, subject to fits; ob. aged 18. (2) Female, aged 43, normal (3) and (4) both ob. young of smallpox; sex not noted. (5) Female, aged 40; married; insane for some months, aged 33, after birth of second child; several subsequent children without relapse. (6) Female, aged 38; subject to fits since age 12; married and has children. (7) Patient. (8) Stillbirth several years after patient; sex not noted.

It is also worth noticing that in the first published examples of the condition known as Tay's choroiditis (Hutchinson [14])—a grouping of small, palish dots at the central area of the fundus, probably in all cases due to minute "colloid" excrescences, formed on the inner stratum of the choroid (Coats [9]), and usually a senile disease—three sisters were affected, and there was a history of neurosis in the family.

Only the barest reference can be made here to certain other cases in which changes occur at the central part of the fundus, sometimes in association with cerebral failure.[1] The nature and alliances of these have not yet been cleared up.

Of causal relationship between any kind of choroiditis and insanity, of whatever kind, there seems to be very little published evidence. The only case I have hitherto come across is one by Wintersteiner [38], where a single spot of black pigment nearly as large as the optic disc was found in the upper inner part of the R. fundus of an imbecile; even here the patch, although perhaps congenital, may have had no connexion with the cerebral defect.

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[1] Mayou and others [20], F. E. Batten [2], Nettleship [27], Edgar A. Browne [5], Best [3], Stargardt [36].

Other varieties of choroidal disease are known to occur as family affections,[1] either limited to siblings or occurring in successive generations, and some of them are thought to be congenital; but the examples already given include all that, so far as I am aware, have hitherto been connected with neuroses of any kind.

Little more than bare reference can be made to certain rare cases recently described, in which cataract develops in association with progressive disease of the nervous or muscular system. I have no personal experience of such cases. One such family has been published by J. G. Greenfield [11], another by Ormond [29], another by Lange [15] is mentioned by Greenfield [11][2], and a fourth is recorded by Arthur S. Hamilton [12]. In 1889, Bock [4] published an account of five sporadic cases of cataract (4 ♀, 1 ♂), coming to maturity quickly, soon after an illness which the author considered to have been meningitis. These patients were aged 34 to 39 years. We have, lastly, Ormond's paper [30] showing the great frequency of lenticular opacities in Mongolian idiots. In a few of this series there was disease of choroid and iris.[3] All the cases of cataract referred to in this paragraph must be distinguished from the common stationary, congenital, lamellar or zonular cataract. Lamellar cataract, when not hereditary, is sometimes associated with congenitally defective mentality of various degrees in the cataractous subject, but when cataract of the same type is hereditary there are seldom any neuroses either in the affected or unaffected members of the genealogy.

CONCLUSIONS.

1. The pedigree which forms the basis of this paper shows an association between mental deficiency and ocular defects, partly developmental and partly morbid.

2. Amongst the members of this family, who are not known to have had any defined mental or bodily disease, a large proportion have been

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[1] Several references are given in the Bowman Lecture [21]. A new case has been recorded by A. W. Stirling [37].

[2] After this paper was in print, in a letter of March 3, 1913, Dr. Greenfield told me he had since seen two additional cases in which myotonia and cataract occur in the same genealogy, one with Dr. Hertz at Guy's Hospital, the other a patient of Dr. Head at the London Hospital. [Published by E. G. Fernsides in the *Proc. Roy. Soc. Med.*, 1912, vol. v, p. 77.]

[3] In Case 9 of Ormond's series there was pupillary membrane in L. eye; Case 14 had high myopia with extensive and highly pigmented choroiditis; Case 2*a* was myopic with choroidal changes limited to each macula; Case 5*a* had corneal opacities with keratitis punctata and subnormal tension. (Letter from Mr. Ormond, October 7, 1912.)

recipients of Poor Law relief, showing that they were not well enough endowed mentally and physically to compete successfully in life.

3. The mental deficiency in this family tends to appear at an earlier age in each succeeding generation (anticipation); but anticipation cannot be proved for the ocular defects.

4. Anticipation may be well illustrated by cases of diabetes, of which some fresh instances are given in Part II.

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A CASE OF PROGRESSIVE LENTICULAR DEGENERATION.

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SINCE May, 1910, there has been under my observation, from time to time, a patient whose symptoms were such as I had never seen before, or had found described in any medical publication. The case was evidently one of a progressive degeneration in some portion of the brain, and I described it in my notes as "rubrocerebellar degeneration." On reading the excellent paper by Kinnier Wilson in *Brain,* March, 1912, on "Progressive Lenticular Degeneration: a Familial Nervous Disease associated with Cirrhosis of the Liver," I saw at once that my case, which had been such a puzzle to me for over two years, was very similar to the cases described by the author, with one very important exception, namely, that the duration of the illness was already over twice as long as any of the other cases which were recorded. The extreme rarity of these cases, only twelve as yet having been published, imposes upon me the responsibility to give at once an account of this patient, especially as a consideration of the case brings forward some new points for discussion, and indicates that some of the views taken from a study of the previous patients may require some modification.

HISTORY OF THE CASE.

The patient was born in 1876, so is now aged 36, and was the sixth child in a family of eight.

Family history.—The father died fourteen years ago at the age of 64, of "cancer of the throat." He was a particularly healthy man. The mother is now aged 74 and is in good health, and seems to have enjoyed this all her life. She has had eight children and no miscarriages. The family is as follows: Daughter, aged 47, born in 1865, in good health; daughter, aged 45, born in 1867, in good health; daughter, aged 43, born in 1869, in good health; daughter, aged 41, born in 1871, in good health; son, aged 38, born in 1874, suffering from heart disease; son, aged 36, born in 1876, the patient; son, died in infancy, born in 1878 (?); daughter, aged 31, born in 1881, in fairly good health, but suffers from colitis.

Previous history.—The present illness began when the patient was about the age of 19, and a careful inquiry into his history before this age has been made. He had no serious illness up to the age of 19, except the ordinary ailments of childhood. He was an exceptionally bright boy, very intelligent, and won prizes and scholarships while at school. He could learn his lessons with very great ease, but was often lazy and did not trouble to do them. He always had a very bad temper and used to get into violent fits of rage when a small boy. After leaving school he occupied himself with electric engineering until the age of 17. He got on brilliantly at first, but then became lazy and for this reason was dismissed by his employers. He then worked in the brass trade for three years, but did not do well, and did not earn enough to keep himself. Since then he has done no work at all.

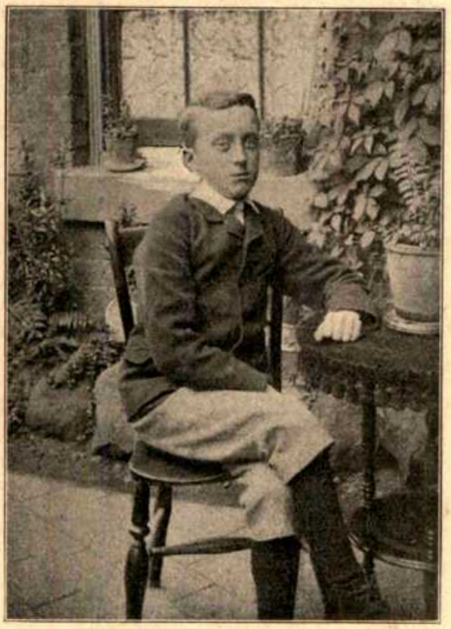

FIG. 1.—The patient as a boy.

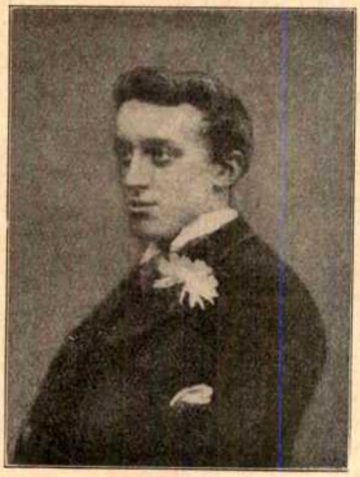

FIG. 2.—Aged 17.

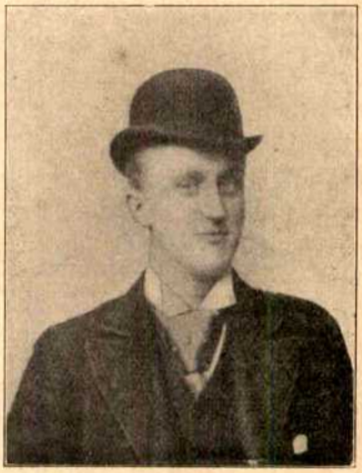

FIG. 3.—Aged 20. The disease had already begun.

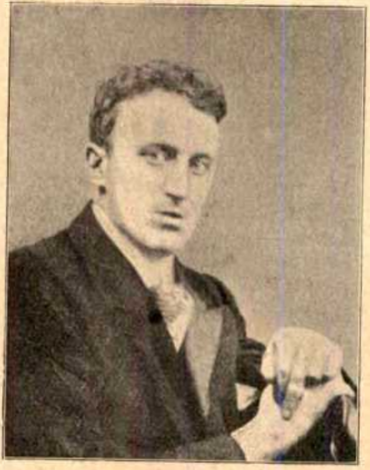

FIG. 4.—Aged 26. The fingers of the left hand appear to be pressed firmly against the back of the right hand, probably to overcome the tremor.

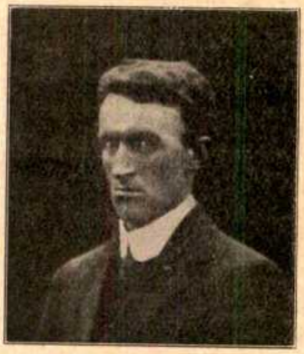

FIG. 5.—Whitsuntide, 1911, aged 35. The change in the facial expression is well marked. He is much thinner than formerly.

The photographs here reproduced show that he was a bright, intellectual-looking boy, and with rather handsome features. His facial expression has considerably altered since the onset of the disease (figs. 1 to 5).

History of present illness.—The first symptoms of the disease appeared at the age of 19, when it was noticed that his right hand trembled considerably, and that the right leg often "went off" in jerky movements when he was sitting. The trembling of the right hand was considered at first to be due to excessive smoking of cigarettes, and later it was thought to be due to St. Vitus's dance. It was also noticed that the trembling increased whenever he attempted to do anything with his right hand. Ever since that time there was a change in the handwriting. It became shaky, and the lines were uneven.

About the time of the commencement of the disease, whether a little before or just after its onset is uncertain, the patient was thrown from a horse and dragged for a little distance on his back, his foot being caught in the stirrup. The patient probably exaggerates in his account of this accident, for he does not seem to have been hurt, because he was able to walk home. The patient's statements are not to be relied upon, and the history which is here given has been obtained from two of his sisters, who do all they can to give me accurate information about him.

About the age of 21 he was staying in Manchester with one of his married sisters, and there is no doubt that this visit occurred well after the beginning of the symptoms. One day he was missing for some little time, and was eventually found sitting on the closet in the yard, and in a very dazed state; he could not speak, and sat staring before him. He was led into the house, but was unable to speak for a few days. His sister's husband accused him of being drunk, and at that time there is a suggestion that he used to drink rather heavily. I think there is some doubt about this, for he was very tremulous at this time, and his hands were shaky, so that those symptoms, which were probably due to the disease, may have suggested alcoholism to his friends. His speech often became "like that of a drunken man."

There is no history of him ever having had a fit, or loss of consciousness before the early symptoms developed, and it was not until two years afterwards that there was any evidence of loss of consciousness.

Jerky movements very early made themselves manifest in the left arm and leg, although at first only the right side was affected. The speech became noticeably altered about two years after the onset. It became very slow, and when he was about 25 it was often impossible to understand what he said. The jerky movements and the difficulty of speech gradually became worse, and then it was noticed that his movements were very slow, and that it was often a very long time before he could commence to do any particular movement. It was difficult for him to get up out of a chair, and took him sometimes two or three minutes before he was able to move. He would then get up quickly, but on standing would sway about, and it would be some time before he could commence to walk, but when he did start he could walk long distances. His muscular powers did not seem to fail him at all; in fact he was remarkably strong.

He became much more irritable, and used to easily lose his temper, and would sometimes attempt to strike one of his sisters who was constantly with him. She nearly always used to know when he wanted to strike her, and she had time to get away before he could commence to make the necessary movements. Sometimes the movements took so long before they could be accomplished that his anger passed before he struck, and then instead of being violent he would break into a good-natured smile.

His facial expression gradually altered, it became "fixed," and often when he attempted to do anything with his hand his mouth would slowly open and be drawn slightly to the right side, the tongue being protruded gradually. His eyes became very much more prominent, and his face during repose lost all expression.

He understood everything that was said to him, and his memory remained very good. He could read a book, and enjoy a joke. His smile used to come very slowly, and remained for a long time, two or three minutes, after which it gradually faded.

This is the history up to about ten years ago. About that time he came home one day staggering very much and in a dazed condition and his sister first thought he was drunk; he fell into a chair and could not speak. He was seen by a doctor and put to bed, but he seemed in his usual health the next day.

From this time, however, all the symptoms gradually became worse. The movements were slower, and the tremors more marked. The speech was more affected. When he got up from the sitting position it was necessary for someone to support him until he could commence to move, but when he once got started he could walk for miles. He often asked people to alter the position of his limbs for him. It was noticed how very stiff all his limbs were, and there is no doubt that it was this stiffness which made him fall over when getting up from a chair.

He has not been able to put himself to bed for ten years, as he was not able to take his trousers off. This was done for him and then he used to be rolled into bed, when it was some little time before he could straighten himself out and lie in a natural position. He sometimes passed urine in bed, and this was probably from laziness, as it meant a great effort to get up. He used frequently to complain of pain in his back, and sometimes in the calf of his leg. His intellectual powers have been good throughout.

His appetite has always been good, but he took a very long time over his meals as mastication was a very slow process. Latterly he often had to be fed, as he would take an hour over a simple meal. The amount of saliva became very excessive, and it ran from his mouth almost continuously. He never had jaundice, and there have been no symptoms which would indicate in the slightest degree that there was any cirrhosis of the liver.

This brings the history up to the time when he first came under my observation in May, 1910, and I will only give a short description of his condition at that date, as it has not very materially altered since then, except that some of the symptoms have developed a little more.

On May 7, 1910, the patient consulted me in order to be admitted into the Royal Home for Incurables, Leamington, for which institution I am the medical examiner in Birmingham. Recognizing the interest of the case, I did not recommend him for admission to the home, but persuaded him to attend as an out-patient at the General Hospital. The rigidity of the limbs was then most marked, and I recorded especially the stiffness of the muscles of the neck. When suddenly asked to look to either side he did not attempt to turn his head, but only his eyes. There was a jerky tremor of the hands, increasing with volitional movements. Clonic movements of the lower limbs developed when they were placed in certain positions. He was unable to stand at first when rising from the sitting position, and this was obviously due to the stiffness of the muscles, which soon wore off if he were supported. He then had no difficulty to stand or walk.

The face seemed to have lost all expression, and in my notes I compared it to the Parkinson's mask. His eyes were rather prominent, the sclerotics showing all round. The movements of the eyes were normal, and the eyes could be moved quite easily, and in this way differed from any other movement he was asked to make. The pupils were equal, reacting to light and accommodation. There was no optic neuritis. The extrinsic muscles of the eyeballs seemed to be the only voluntary muscles not affected by the pseudo-spasm. When the patient smiled he did so very slowly and stiffly, and the smile lasted a long time before it passed off. In this the condition differed greatly from paralysis agitans. The tongue, of which there was no tremor, would be protruded very slowly and not very far. Swallowing appeared normal, except that it took him a long time to eat a meal. The speech was difficult to understand, as each syllable was very drawn out, and it took him a long time to say a short sentence. The intellect appeared normal, but he was rather emotional. The hands were held in the position characteristic of paralysis agitans, but the tremor of the hands was far coarser and not at all like that which is present in this disease. The grip of the hands appeared rather feeble. The flexor muscles of the limbs were more affected with the stiffness than the extensors. No paresis nor paralysis could be ascertained.

The abdominal reflexes were brisk, also the knee-jerks. The ankle-jerks were brisk, and an ankle-clonus could be obtained although it lasted for only about half a dozen jerks. It was not a true ankle-clonus. A plantar extension on each side was obtained, although with difficulty, but there is no doubt that it was present at this time.

The sensation appeared normal, but he complained of a little pain in the lower part of the back, and also in the calves of the legs.

Dysergia or dysmetria was tested for in the manner recommended by Tom A. Williams, in the *Quarterly Journal of Medicine,* vol. iii, p. 343, but the patient made the lines very slowly, and always stopped at the right place.

The chest and the abdomen appeared normal upon examination, and there were no symptoms pointing to any gastric derangement. The bowels were regular. The urine normal, but the radial arteries were slightly thickened.

After attending as an out-patient for a few times he was admitted as an in-patient under Dr. Stacey Wilson. No additional light was thrown on the case, but the presence of an extensor plantar reflex on each side was confirmed.

The case puzzled me greatly, and all those to whom I showed him. The diagnosis of rubrocerebellar degeneration was made. The patient was admitted into the Royal Home for Incurables at Leamington in November, 1910, where he stayed about a year. He became very restless and dissatisfied there, and left of his own accord and against advice.

I did not see the patient again until the end of August of this year [1912], and then considering him to be a case of progressive lenticular degeneration, he was admitted as an in-patient to the General Hospital under Dr. J. W. Russell, who very kindly placed a bed for him at my disposal, in order that a more thorough examination could be made.

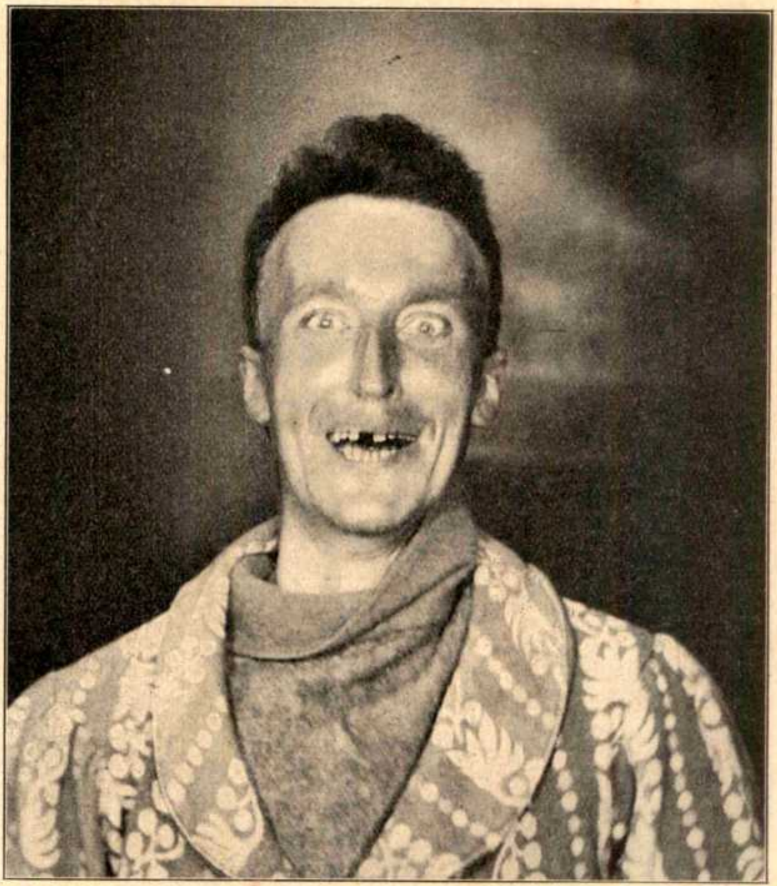

FIG. 6.—Characteristic smile. Exposure, 10 secs.

CONDITION OF THE PATIENT IN SEPTEMBER, 1912.

The patient is a well-developed man, about 5 ft. 7 in. in height, and weighing 9 st. 7 lb. Examination of the heart, lungs, and abdomen shows nothing abnormal. The liver dulness extends from the sixth rib in the right mammary line to the costal margin. There are no symptoms pointing to cirrhosis of the liver. The urine is normal.

When the face is in repose it appears very wanting in expression, and has a vacant but not a silly or fatuous look. The want of facial expression contrasts very acutely with the intelligent look in the eyes, which appear bright and humorous.

There is apparently no loss of intelligence. He is rather emotional at times, and frequently gets angry without any cause. He is usually in a very happy frame of mind, and it is quite easy to obtain a most delightful smile from him. His smile is most ludicrous, and infects everyone with laughter who looks at him. It comes very gradually, stays there a long time and then gradually fades. Fig. 6 is a good photograph of this smile, and indicates the slowness of the movements of the muscles of the face, as the photograph had an exposure of ten seconds. He laughs stiffly and in a subdued manner, but always as though he greatly enjoyed the joke. This peculiar laugh is evidently due to the stiffness of the facial muscles. There is no explosive laughter. At other times he becomes very depressed, but while in hospital he has always been good tempered, which is quite different from when he was at home, for there he frequently went into violent fits of rage. He can read the newspaper quite well, and takes interest in all passing events. He has no delusions nor hallucinations, as far as can be ascertained.

Eyes.—The ocular movements are good, and the eyes move in any direction quite quickly. The pupils are equal and react to light and accommodation. There is no nystagmus. The sight is good and the optic discs are normal. There is a considerable retraction of the lids which makes the eyes appear prominent, and suggests that a slight amount of exophthalmos is present. The sclerotics show all round, and von Graefe's sign is present. The upper eyelids are very difficult to evert. The amount of retraction of the eyelids varies considerably from day to day, and often becomes more obvious while talking to the patient, or while he is attempting to make some movement, or to speak. If he is excited the eyes become very much more prominent. If asked to close the eyes he can only do so after a short interval, and when they are closed it takes some little time before he can open them. The corneal reflexes are, however, quite brisk.

Face.—The muscles of the face move very stiffly. The mouth when opened is done so slowly, and when he attempts to speak the lips are often slowly pursed up, almost as though he were going to whistle before he can produce a sound. At other times when he is attempting to do any movement, specially when he tries to write, his mouth becomes drawn to the right side and the tongue slowly protrudes, while he breathes heavily, making a kind of snorting sound (figs. 8 and 9).

The mouth is often held open in a most rigid manner, and saliva dribbles excessively from the mouth. When he takes liquids to drink they have a tendency to run out of the angles of the mouth. The tongue when protruded is usually inclined towards the right, and is very tremulous. The movements of the tongue are very slow. He is

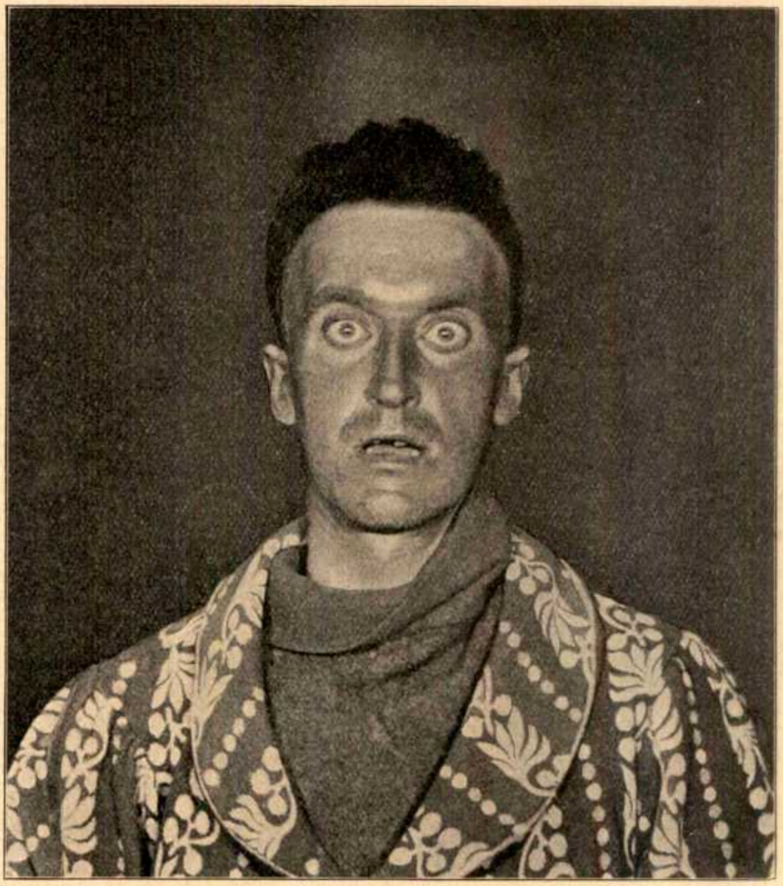

FIG. 7.—The face is in repose. There is great loss of expression. The eyes appear prominent owing to the retraction of the eyelids. The mouth is habitually kept slightly open. Exposure 8 secs.

able to masticate his food, but this is done very slowly; the act of swallowing is quite easy.

Speech.—There is marked dysarthria. At times it is quite impossible to understand what he says. At other times the speech improves, and he is fairly easily understood. The syllables are greatly drawn out and there is a long interval between each word. Each syllable is so drawn out and so extended that it is frequently unrecognizable. The word "no" may last almost a minute when the speech is very bad, and then one is left in doubt whether he has not said "yes." He is unable to make any signs with his hands to indicate what he wants, and he often gets into a temper because he thinks people are stupid in not understanding him. The soft palate moves well on attempting to phonate, and the palatal reflex is brisk.

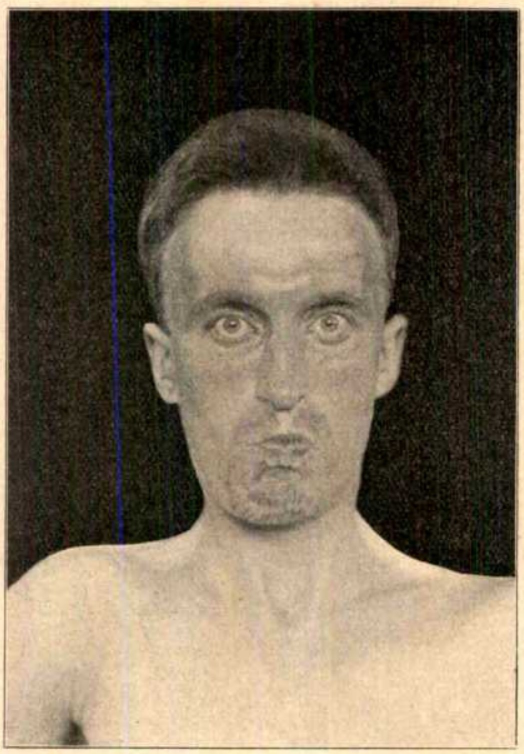

FIG. 8.—The patient is attempting to say a word. The pursing up of the mouth is well marked. Exposure, 4 secs.

Hearing is normal, and as far as can be ascertained there is no defect of sensibility over the face. It was found impossible to determine if there is any alteration in taste.

Motor system.—The neck and shoulders are held very rigid. There is great hypertonicity of the muscles, and frequently the right platysma contracts very forcibly. There is no wasting of the voluntary muscles, and there appears to be no loss of power. In fact he is a muscular man. The arms are very rigid and the hands are held in the position characteristic of paralysis agitans (fig. 10). The hypertonicity affects the flexor and extensor muscles equally. The stiffness is not very marked in the fingers, but this varies considerably. A remarkable feature is that the stiffness of the limbs varies in degree from time to time. If an attempt is made by an observer to move the arms, at first they appear very rigid, just as if the patient were resisting, and then after a few movements they become more flaccid. However rigid the arms may be, the patient can always move them on being asked to do so, but it takes

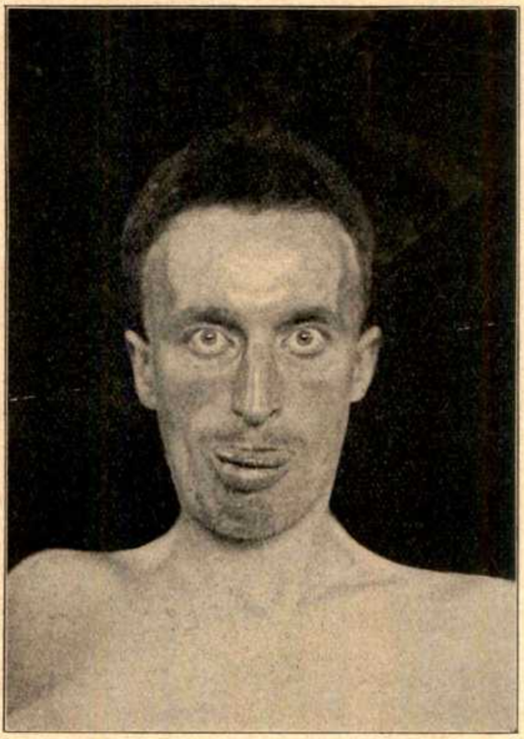

FIG. 9.—The tongue is protruded slightly to the right, and the lower lip is everted. The patient was preparing to get up from the chair. Exposure, 5 secs.

some time before he can commence the movement. After the movement is commenced it is often quite rapid. The grasp is fairly strong and equal on the two sides. He will, however, grasp the hand quite slowly, and then it takes a little time before he can loose hold. He can often move one arm before he can get control over the other, and then he pulls the other arm to where he requires it.

The legs are in a similar condition to the arms. The rigidity does not disappear during sleep. If an attempt is made to move the arms while the patient is asleep they are found to be quite rigid, and any forcible attempt to move them wakes the patient at once. The same condition is found in the neck and legs.

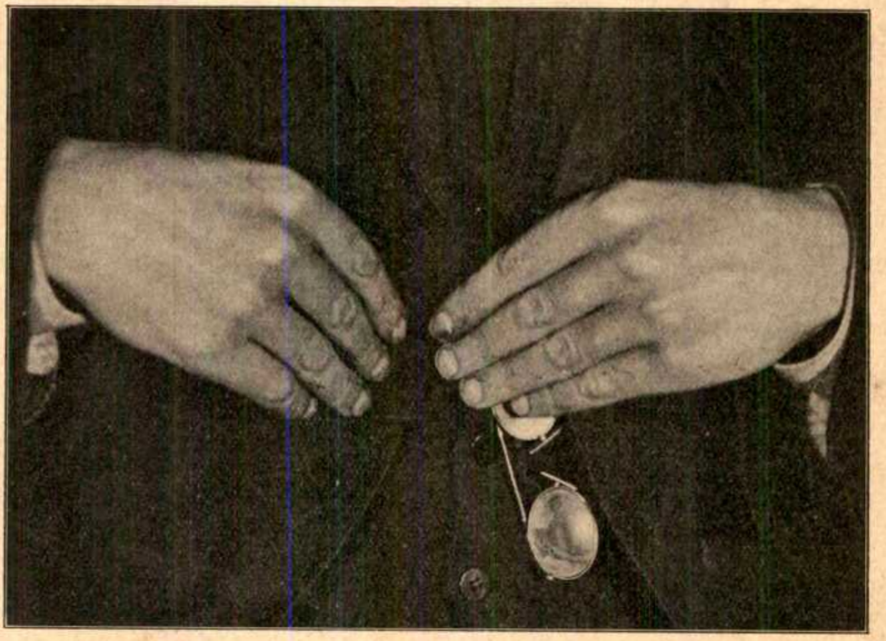

FIG. 10.—Showing the characteristic position of the hands, suggesting paralysis agitans.

(*a*) *Contractures.*—There are no true contractures. The arms are always flexed at the elbow-joint but can be overcome by passive movements. The wrists are held flexed and the forearm pronated, but these positions can always be overcome. The legs are kept slightly flexed at the hip and knee joints, and the feet extended, but all these positions can be overcome by passive movements.

(*b*) *Involuntary movements.*—The patient will lie in bed for a long time without any involuntary movements, but often without any warning one of the legs may commence rhythmical involuntary movements, at first slight, then becoming more exaggerated, and then quite riotous in their intensity. These movements are rhythmical and alternating flexion and extension. The same movements occur in the arms. The movements are wide, about four or five a second. There is frequently a less coarse tremor in the hands, which consists chiefly in alternating flexion and extension of the carpo-metacarpal joints. The tremors occur in the limbs on each side of the body equally, but the tremor is often confined only to one limb. It increases with excitement and also upon exertion. The tremor varies in severity from day to day, but there is always a slight tremor present. Some days the tremor becomes very severe, and this is especially so when the patient is sitting in a chair or sitting up in bed with the legs drawn up. When in these positions the whole body may be affected. There is a rapid to-and-fro movement of the head and body; the hands are held in front with the elbows at right angles, and there are alternating flexion and extension movements at the elbows and wrists, and similar movements at the knee and ankle joints. There are frequently rapid adduction and abduction movements at the shoulder and hip joints. These involuntary movements are rhythmical and occur at the large joints, and may continue for hours and even a few days, becoming quite riotous at times. The movements are equal on the two sides, and all of them are at the same rate, keeping time together. They are not athetoid nor choreiform in character, but consist of a rhythmical and alternating contraction of muscular groups and their antagonists. There is no ataxia.

(*c*) *Standing and walking.*—When the patient is got out of bed, a process which he is unable to do without aid, and placed upon his feet, he cannot keep his equilibrium at first without support. He would fall over, and this is obviously due to the rigidity of the muscles of the legs and trunk. He often asks for one of his legs to be moved for him. Before beginning to walk he usually stands on his toes, and then the rigidity is slowly overcome and he can get his foot flat on the floor (fig. 11). After a time, varying from half a minute to two or three minutes, he can begin to walk. He steps off quickly and can walk at a good rate and for a long distance when he has got started. He reminds one of a mechanical toy in the way he walks. The movements are rapid and jerky. When walking he is unable to turn suddenly round, but always turns in a wide circle. On standing still there is seen to be a slight to-and-fro tremor of his head, shoulders,

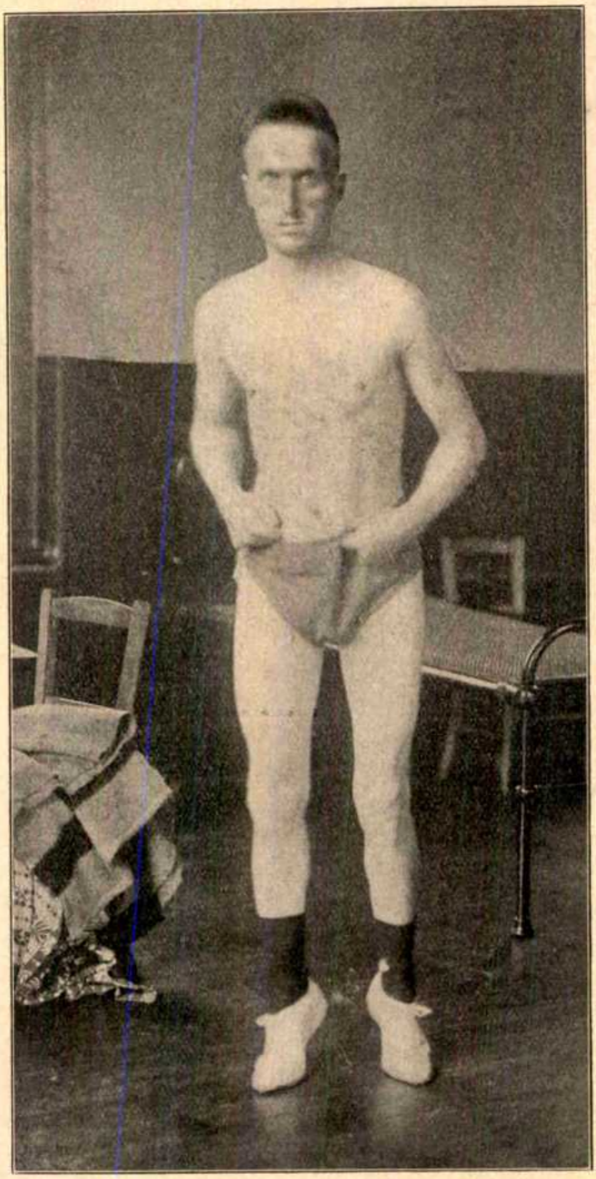

FIG. 11.—The patient has just been placed upon his feet. He has gained his equilibrium, but is unable to get the heels on the ground. The attitude of the hands is characteristic; they are pressed against the body to overcome the tremor. Exposure, 4 secs.

and body, and there is a tendency for him to fall backwards, which makes him constantly take a few steps back to prevent himself falling. He stands with his legs apart and sways a little backwards and forwards. Closing the eyes does not affect his equilibrium. Retropulsion is very marked. When helped back into bed, he rolls in with his back bent forwards, his legs drawn up, and his head bent forwards. He will lie on his back in this attitude, his head not touching the pillow, and his heels not in contact with the bed. After about half a minute he can lay his head on the pillow and get his heels down.

Writing.—It is a most interesting sight to see him write. He firmly grasps the pencil and presses it forcibly on the paper. He then seems to contract most of the muscles of his body. His mouth becomes pursed up, a most determined expression appears in his face, the tongue gradually protrudes, and he makes a kind of snorting sound. He writes very slowly, but the wrist appears to be glued to the paper, and to act as a centre of a circle, so that he will write two or three words in a straight line and then the rest will be placed in a semicircle towards the right.. Then he will begin a fresh line, placing the wrist a little further down. The writing is quite clear and the letters well formed. By pressing firmly with the pencil on the paper the patient can usually overcome the tremor of the arm, but some days he finds it impossible to do this. He will then write a few letters and then the tremor will overcome him, and the pencil move up and down the paper recording the excursions of the tremor. In order to stop the tremor in the hand he will often place the left hand firmly on top of the right. In fig. 12 the last four words were written in this way. The sentence took fourteen minutes to write.

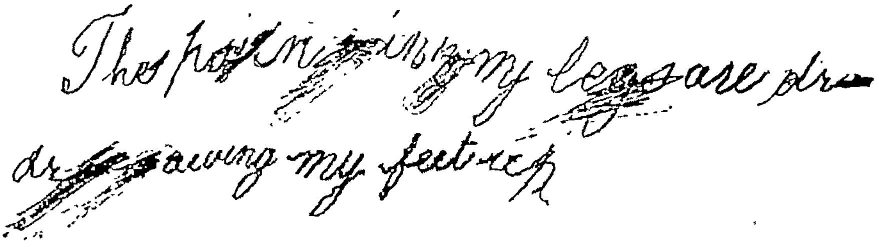

FIG. 12.—The pencil was firmly pressed on the paper to overcome the tremor; but at intervals it is seen that the patient lost control of his hand, and here the pencil records the tremor. The whole sentence took fourteen minutes to write.

Reflexes.—The arm-jerks are brisk and equal on the two sides. The abdominal reflexes are remarkably brisk. The knee-jerks are normal and equal on the two sides. The ankle-jerks can easily be obtained. There is no true ankle clonus. The plantar response is flexor and equal on the two sides. The sphincters are unaffected.

Sensory system.—As far as can be ascertained, there is no change in sensibility. It is extremely difficult, and takes great patience to determine the condition of sensibility, as the patient can only with very great difficulty indicate when he appreciates any touch. Two years ago I carefully examined him in this respect, and convinced myself then that there were no sensory changes to the usual tests. Even at that time it was a most laborious process. He frequently complains of pains in his back and legs, which seem to be of the nature of cramp.

The patient was in hospital for about one month, and during that time there was no progressive increase in the symptoms. There was no loss of weight, and no diminution in the muscular power. Some days he appeared very much better than others, and this was chiefly noticeable in diminished muscular rigidity, and improvement in the speech. He improved when he was left entirely alone, and not excited by being examined.

There was no evidence of syphilis, either acquired or congenital, and the Wassermann reaction was not present in the blood or in the cerebrospinal fluid.

I could find no method whereby to ascertain if there be any impairment of the functions of the liver.

There is no doubt but that this case is similar in most respects to those described by Kinnier Wilson as "Progressive Lenticular Degeneration: a Familial Nervous Disease associated with Cirrhosis of the Liver." The case appears to correspond to a bilateral degeneration of the lenticular nucleus. It is obviously an extrapyramidal motor disease, for the reflexes are normal. It evidently bears a close resemblance to paralysis agitans, in the facial appearance, the position assumed by the arms and hands, the rigidity, and to a slight extent in the tremors and the retropulsion.

This case differs in the following way from those described by Kinnier Wilson.

(1) *Age of onset.*—The age of this patient at the commencement of the symptoms is certainly later than most of the recorded cases. In many the symptoms began in childhood.

(2) *Duration of the illness.*—The disease has now been manifest for seventeen years, whereas in all the others there was a fatal termination within seven years. In one case the duration was only four months. There is no reason to suppose but that this patient may not live many years longer.

(3) *Tremors.*—The tremors are always present, but vary in intensity from day to day, whereas in the recorded cases when they had developed they never seemed to diminish.

(4) *Rigidity.*—The muscular rigidity does not appear to have been less on one day than another in any of the recorded cases. In this patient the rigidity never disappears, but it varies in intensity from day to day, and also while under examination the rigidity changes distinctly in different parts of the body. A limb which is at one time extremely rigid may at another become comparatively flaccid.

(5) *Contractures.*—There are no true contractures in this case, and these were such a marked symptom in all the other cases when the disease had been present even for a short time.

(6) *Dysphagia.*—There is no dysphagia in this patient, only a difficulty in mastication.

(7) *Emaciation and weakness.*—There is no emaciation nor weakness. The patient is not fat, but he is quite strong.

The nervous symptoms present in this patient leave no doubt that the lesion is situated bilaterally in the lenticular nucleus; but, unless there be cirrhosis of the liver, the disease would not be considered by Kinnier Wilson to be identical with that which he described. It is difficult to imagine that the patient has been suffering from cirrhosis of the liver—a cirrhosis of the multilobular type—for so long as seventeen years, however insidious its onset and slow its devolopment, without producing some of the symptoms associated with this affection of the liver. It is quite easy to understand that cirrhosis would not produce symptoms in some of the published cases in the short time from the onset of the disease to the fatal termination. The author in his description of the disease considers that the cirrhosis of the liver is essential for a diagnosis of this affection. The type of cirrhosis which he describes is identically the same as that which occurs in the common "hobnailed" liver. In the "hobnailed" liver actively regenerating areas are always found, and similar regenerating areas in the cirrhosis associated with progressive lenticular degeneration are considered by the author to explain why the liver condition may last so long and produce no symptoms. Nevertheless the same condition of the liver, as far as can be ascertained by careful microscopical examination, when occurring in an individual unaccompanied by this nervous disease, nearly always produces definite symptoms, and is usually very soon fatal. If the cirrhosis of the liver had commenced early in the disease of these cases of lenticular degeneration, it is extremely difficult to imagine why it did not produce death earlier. The author suggests that the cirrhosis is in all probability a primary feature of the pathology of the disease, and that the toxin which produces the degeneration in the brain "is associated with the hepatic cirrhosis, and may be generated in connexion therewith." This means that the toxin is generated in the liver. Is it not much more probable that the toxin is generated in the intestines, and that its absorption produces the lenticular degeneration primarily, and that it is not until some time after this has occurred that the toxin is sufficiently potent or has had sufficient time to produce the cirrhotic changes in the liver? In other words, may not the cirrhosis be a much later change than the degeneration in the brain? In my case therefore the toxin, whatever be the cause of its development, may have picked out the lenticular nucleus, and may not even as yet have affected the liver. If this be true, should the patient die now from some intercurrent affection and show at the *post-mortem* examination a bilateral degeneration of the lenticular nucleus, the absence of a cirrhotic liver would not necessarily prove that the disease was not identical with that described by Kinnier Wilson.

The nervous manifestations are obviously progressive, and therefore the toxin which is causing them is still being formed, and if the patient lives until his life is terminated in the same manner as the cases already described, by that time the toxin may have produced the cirrhotic changes. The poison probably must reach a certain degree of toxicity before it causes the lenticular degeneration, and even to a higher degree of toxicity before it can make that degeneration sufficient to be fatal. It is probable that this higher degree of toxicity must be reached before the hepatic cirrhosis can be produced, and therefore the hepatic cirrhosis may be a late morbid change in this disease.

In support of the view that the toxin is not of hepatic origin, but that it is generated elsewhere and causes morbid changes both in the lenticular nucleus and in the liver, may be cited the action of well-known organic and inorganic poisons. The virus of syphilis produces well recognized changes in the brain and spinal cord, and at the same time causes affections of other organs of the body, such as atheroma, cirrhosis of the liver, fibrosis of the lungs, &c. The diphtheria toxin may cause changes in the nervous system and also in the musculature of the heart. Lead is well known not only to act upon the peripheral nerves, but it is also commonly considered to be a cause of interstitial nephritis. Other poisons are known to behave in a similar manner, and therefore it is quite legitimate to presume that the toxin in progressive lenticular degeneration may not only have a selective action upon the lenticular nucleus but also upon the liver, and that the toxin may be generated elsewhere than in the liver. If this be so, it is quite possible for the toxin to produce the lenticular degeneration before it causes the hepatic cirrhosis.

Dr. S. A. Kinnier Wilson has kindly examined this patient with me, and reported as follows:—

"The clinical picture presented by his patient offers the very closest analogies to that which I have seen and described in four cases of progressive lenticular degeneration. The combination of tremors, rigidity, and true hypertonicity, dysarthria, contracture-attitudes, the absence of any sign of pyramidal involvement, and the state of the reflexes, establish the case as essentially one of extra-pyramidal motor disease, and there can be, in my opinion, little doubt that from the pathological point of view the lesions are situated in, or at least involve, the corpus striatum and subthalamic region on both sides.

"Nevertheless, in certain particulars which seem to me to be important, the case differs from those already described.

"(1) The age of the patient and the known duration of the disease are not such as have hitherto been observed. Of course where only a comparatively few cases in all have been recorded, one must be prepared for a variation such as this patient presents; nevertheless, the duration of the disease is much longer, no less than some ten years or more, than in any previously recorded instance.

"(2) Notwithstanding the great duration, there are as yet no signs either of emaciation or of contracture. When it is remembered that these have been prominent, and sometimes even early symptoms in every one of the known cases, I cannot but think that their absence constitutes an important distinction.

"(3) The actual form of involuntary movement presents certain peculiarities. The tremor is far from constant, although when it occurs it is typical in character. In the four cases described in my paper, the tremor was not only constant, but increased in severity with the progress of the disease. In Dr. Sawyer's patient there is occasionally a spasmodic movement of the lower facial musculature that resembles the 'mobile spasm' of Gowers, and may well be described as athetoid. There is also, on occasion, a more or less similar movement of the hands, which may be more fairly characterized as athetoid than tremulous.

"In one, or perhaps, two, of the recorded cases, it is true, a not dissimilar movement was observed; these were, however, notably acute cases, and in all the chronic cases that have been recorded, and that I have personally seen, the involuntary movement was one of never-ceasing tremor.

"(4) Occasionally the hypertonicity of the patient's musculature relaxes, when the limbs become flaccid, and even hypotonic. This was the case when I had the opportunity of seeing Dr. Sawyer's patient, in his hands and fingers; and one was surprised to find that the fingers could be notably hyperextended by passive movement where a moment before they were rigid and in a contracture attitude of flexion. Again, this cannot be regarded as an essential point of difference from a diagnostic standpoint, but I have not seen such changes in my own cases.

"(5) The dysarthria of Dr. Sawyer's patient is a long drawn-out, almost staccato utterance, which is not identical with that which I have seen myself.

"In mentioning these points, my desire has been not to magnify any possible differences, but to demonstrate in what way the patient presents features that have not hitherto been noted as occurring; and there does not appear to me, perhaps, to be any inherent reason why such symptoms should not also be regarded as belonging to the syndrome. I attach importance, however, to my first two points, and, in view of the apparently inevitable way in which the malady has steadily progressed in all the recorded instances of progressive lenticular degeneration, as well as in all the cases personally observed by myself, I venture to take leave to question whether in Dr. Sawyer's case we are dealing with identically the same disease, *i.e.*, a hepatitis with subsequent cirrhosis and a concomitant progressive degeneration of the lenticular nucleus."

A CASE OF PERIODIC PARALYSIS.

BY H. WILLOUGHBY GARDNER, M.D.
Physician to the Salop Infirmary.

One day in the spring of 1907 there came to my out-patient room a big, hulking, lazy-looking youth, aged 17, accompanied by his mother, who gave me the curious history that for the last two years he had been subject to attacks of complete loss of power in his arms and legs. I could find nothing wrong in any way with the lad, and was inclined either to disbelieve the story, or to put the condition down to mere laziness, or at most to hysteria.

However, they came again two or three times with the same story, and told me that the attacks were becoming more frequent and severe, and that their fear was that he would become permanently paralysed. The possibility of periodic paralysis then occurred to me, so I arranged that on the occasion of the next attack he should be brought at once to the Salop Infirmary to enable us to study his condition.

On Saturday, June 8, 1907, a cart drove up to my door with the patient. I found him to be paralysed, so sent him direct to the Infirmary, where he was put to bed. On examining him an hour later I found him to be a typical case of periodic paralysis. The note taken at the time was as follows:—

F. T., aged 17, collier, from the village of Anscroft, near Shrewsbury.

History of attacks.—He has been subject to attacks similar to the present one for nearly two years. The first attack occurred in August, 1905. It came without any warning. He woke up one morning and found that he was unable to move his head, arms and legs. His head ached and so did his back, arms and legs, and he felt weak and ill. The attack lasted all day. During it he was unable to pass water, and his club doctor was sent for, who drew it off with a catheter. Next morning he woke up feeling as well as ever and returned to work.

The second attack was precisely similar, and occurred nine months later [May, 1906]. The third attack occurred six months after the second. The fourth attack after an interval of another three months.

The fifth attack after an interval of another two months. The sixth attack after an interval of one month only.

An interval of two weeks only had intervened between the sixth attack and the present one—the seventh. Not only had the attacks come more and more frequently, but they were also more prolonged; the sixth attack began on a Sunday morning and lasted three whole days. On the Wednesday morning when he woke up he found himself quite well once again.

Previous history.—He had never had any illness, had not suffered from infantile convulsions; he had been a strong healthy boy, fairly intelligent, leaving school in the fifth standard, never nervous or delicate in any way. He had, however, been subject to "sick headaches" for as long as he could remember, generally at intervals of two or three months. His head used to feel heavy; he used to see "zigzag lines and round circles," and the attacks would end in vomiting, relieving the headache. Then he would sleep for two or three hours, and wake up feeling quite well. Since the attacks of paralysis began these sick headaches had ceased.

Family history.—Patient belongs to a strong, healthy family by no means neurotic. His father, mother, five brothers and three sisters are alive and well and strong. One brother died in infancy. His mother and one brother suffer from occasional "bilious headaches." There is no history of any similar attacks of paralysis having occurred in his family, either on the father's side or the mother's, nor is there any history of epilepsy or any other nervous disease.

History and Description of the Attack on June 8, 1907.

Patient woke with a headache at 4 a.m. on Saturday, June 8; he was aching all over, and found that he was unable to move his arms, legs or head. At 2 p.m. he vomited. He felt better after this, but the paralysis was in no way lessened. At 5 p.m. he was admitted into the Salop Infirmary.

His face was flushed and his skin moist; there was slight drooping of the eyelids, such as one often sees in cases of severe megrim. He was perfectly conscious, his mind was clear, and his speech was unaffected. His pupils were equal, not dilated, and reacted well to light and to accommodation. His fields of vision, roughly tested, were normal. The facial muscles were unaffected. He could move his head slightly from side to side, but could neither flex nor extend it. He was just able to move his arms but he could not raise them, and his grasp was very weak. His legs were much more severely affected than his arms. He could move his toes slightly, but could not raise his feet, nor bend his ankles, knees or hips. There was no weakness of the respiratory muscles.

There was no loss of sensation either to touch, pain, or heat and cold.

The knee-jerks and ankle-jerks were completely absent, as were also the deep reflexes in the upper limbs. No muscular contractions could be evoked by mechanical stimulation. The skin reflexes were diminished; the plantar, cremasteric, and abdominal reflexes were all present but feeble, and the plantar was flexor.

On testing with the faradic current no contractions at all could be elicited in the muscles of the legs, and very slight ones only in those of the arms. There seemed to be a similar absence of contractility with the galvanic current, but the galvanic battery was not in a trustworthy condition.

The loss of power, of reflexes, and of electrical contractility was precisely the same on the two sides.

The cardiac apex was just outside the nipple line in the fifth interspace; there was a soft blowing murmur, most evident in the aortic and pulmonary areas. The second sound was feeble. The pulse was regular; its rate was 42; there was no appreciable increase of tension.

He was unable to pass his urine; a catheter was passed and 30 oz. [850 c.c.] were drawn off. His tongue was furred, and his bowels had not acted. He was somewhat drowsy, and complained of headache, and aching of back and limbs. The temperature was subnormal. The specific gravity of the urine which was drawn off was 1030; it contained no albumen or sugar, but showed a trace of indican.

When he woke next morning, June 9, he was able to move his arms and legs slightly; at 8 a.m. the attack was rapidly passing off. When seen by me at 12 noon, he had no headache and no aching of his limbs; his skin was no longer flushed nor moist; his tongue was cleaning; his pulse-rate was 54, and the tension was still low. The cardiac apex was in the nipple line. His eyelids no longer drooped; he had perfect motor power in his arms and legs; his knee-jerks were brisk; and his plantar, cremasteric, and abdominal reflexes were very active, as were also the electrical reactions. Next morning his pulse was 60, and he walked five miles home, apparently in perfect health.

Subsequent Attacks.

The next attack began at home on Monday, July 7, just four weeks later. The evening before he had felt cramps and slight aching whenever he moved. He woke at 1 a.m. feeling that an attack was coming on; at 3 a.m. he got up and tried to walk it off, and partially succeeded. He did not go to work that day, but walked about at home. Next morning, when he woke, he found he was unable to move his arms or legs, though he could move his fingers and his feet. At dinner time he was much better, and was able to get up and pass a large quantity of water; but the paralysis soon came on again, and lasted all the next day (Wednesday, July 9). He woke on Thursday, July 10, perfectly well again.

The next attack began on Sunday, July 20, after an interval of nine days only. He felt that it was coming on the evening before. The attack was but slight and transient, so that he was able to go to church, though feeling some weakness in the calves of his legs. He walked about all afternoon, was able to pass water, and his bowels acted. Next morning, however, he woke up paralysed, and was unable to empty his bladder. As the attack showed no signs of passing off, he was again brought to the Salop Infirmary. When admitted the paralysis of the arms and legs was found to be less complete than on the previous occasion; he had no headache, and did not feel ill. The knee-jerks could be elicited with difficulty; the skin reflexes were present, but greatly diminished, and the same was the case with the electrical and the ideo-muscular contractility. The tongue was clean, articulation and deglutition were normal. The bowels, however, were not open, and the urine, 34 oz. (964 c.c.), had to be drawn off on admission. The pulse-rate was 42, the cardiac apex was outside the nipple line, and there was a soft, systolic murmur as before; the aortic second sound was accentuated, and occasionally a reduplicated second sound could be heard at the pulmonary base. In addition to these signs there was very great weakness of the intercostal muscles, so that respiration was almost entirely diaphragmatic.

Patient woke up the next morning as well as ever, and went home the day after. His pulse-rate was then 52, and his apex-beat in the nipple line. His bowels remained constipated.

Treatment was then begun, and the attacks ceased for over two years. Early in November of 1907 he woke one morning at 4 a.m. feeling that an attack was coming on; at 4.10 he took a dose of his caffein medicine, and at 4.30 he took 4 grains of calomel; at 6 a.m. he got up and walked about, and the attack passed off completely.

Examined on November 20, 1907, his pulse was 72, tension normal; the cardiac apex was in the normal position, half an inch within the nipple line, and there was no murmur.

The next attack occurred one Sunday in December, 1909, after playing a very hard game of football on the Saturday afternoon. He went to bed feeling all right, but woke up on Sunday morning with aching, and great weakness of the arms and legs. He got up and walked about a little, but after his dinner all the use went out of his arms and legs, and he had to be carried to bed. He was completely paralysed all the next day, but woke up quite well on the Tuesday morning.

He came to ask me if he ought to give up football, but I told him to play just as before but to take his calomel pills and a dose of his caffein medicine in the evening after playing; to eat but little supper, and to drink plenty of water. When next I saw him in February, 1910, he had played four equally hard games of football with no ill effect.

After that he gave up all treatment, and I saw no more of him until I visited him on May 11, 1912. I ascertained that he had had five attacks since I had seen him. Two of these were during 1910, the attacks developing each time on a Sunday morning after playing a hard game of football on Saturday afternoon; one attack occurred on a Sunday in August, 1911, after eating a hearty supper of sausages and drinking beer; and two attacks had occurred during the present year, also after playing football.

He is at present in perfect health, and in full work as a collier. He is married, and has one child 2 years old, strong and healthy.

The last few attacks have been characterized by violent vomiting—the vomit being green and slimy and "nasty." After the vomiting the symptoms rapidly cleared up. On one occasion he came home from work and vomited in the same violent manner for about two hours. No paralysis occurred on that occasion.

During the last three attacks he has been very thirsty and slightly delirious. He has had no headaches apart from the attacks of paralysis. His bowels have been very constipated recently, often acting every third day only. His wife volunteered the opinion that beer or stout, sausages and cheese were likely to bring on attacks.

Discussion of the Case.

The points of especial interest about this case seem to the writer to be:—

(1) Though periodic paralysis is usually a family disease, no other members of his family have ever been affected.

(2) The attacks of paralysis seem to have replaced previous attacks of "bilious headache."

(3) Either the attacks themselves or the warnings thereof seem nearly always to have begun on a Sunday.

(4) When the patient was first seen the attacks were occurring at ever decreasing intervals, and were becoming more severe and more prolonged. But treatment seems to have been notably successful.

The disease, though a very rare one, is so curious and so interesting that it has been closely studied by various observers. As far as the writer knows, only four cases have previously been recorded as occurring in Great Britain, an isolated case by Singer and Goodbody [5], and three cases, a mother and two sons, by Farquhar Buzzard [1]. In America, however, a number of cases have been reported, including eleven in five generations of one family, by E. W. Taylor [6], and nineteen in four generations of one family by Holtzapple [4]. Other cases have been reported on the Continent of Europe, notably by Goldflam [2, 3], who reported eleven cases in one family, and by Westphal [7]. Holtzapple has written a particularly interesting account. When he published his paper in 1905 six of his patients had died in an attack, one in his presence. It is stated that necropsies have been obtained in two of his cases since with negative results. Two of his patients became permanently paralysed late in life, by a slow progressive paraplegia, which left the sphincters unaffected. Fourteen members of the family had attacks of paralysis only, five had attacks of paralysis and sick headache, and thirteen others suffered from attacks of sick headache alone. The total number afflicted with either paralysis or headache was thirty-two.

In nine instances the disease was transmitted through the father and in eight through the mother. In some cases the affected parent would have the headaches and the children the attacks of paralysis, or *vice versâ*; in other cases the attacks of paralysis would take the place of antecedent attacks of headache, while in others, again, the attacks of headache and paralysis would alternate. A severe attack of headache seemed to protect for a short period against an attack of paralysis, and it seemed quite evident that the attacks of headache and of paralysis are due to a common cause.

In the present case also the attacks of paralysis took the place of previous attacks of headache. The parents of Holtzapple's cases were of German descent, the father being afflicted with periodic sick headaches. There was no neuropathic family history obtainable on either side.

In the present case there is no history of any similar attacks in any member of the family on either side. The mother was said to suffer from bilious headaches, but she made very light of them, and they evidently were not remarkable either for severity or frequency. There was no neurotic family history, and the patient himself is as far removed in type from the neurotic as it is possible for anyone to be.

A curious thing about the present case was that the attacks, or at least the warning symptoms thereof, nearly always seem to have begun on a Sunday. The reason for this seems either some unaccustomed and violent exercise, such as a football match, or a particularly rich and indigestible supper such as sausages, or a combination of both on the Saturday half-holiday. All the attacks developed during sleep: The patient would wake up and find himself paralysed; in some instances he was able, by getting up and walking about, to throw off the attack, though generally it would come on again with increased intensity a few hours later. In two of Buzzard's cases, though the attacks often occurred during the night, they could, it seems, usually be brought on at any time by taking unusually violent or prolonged exercise and then resting.

Not only is periodic paralysis a family disease, it is also strongly hereditary. Amongst the many well-known hereditary diseases, those which seem most to resemble it are epilepsy, migraine and gout. Epilepsy resembles it in that the attacks are similarly periodic, and tend to appear more and more frequently if their occurrence is not checked by treatment, and they tend to produce in the long run a slow gradual deterioration of the brain, just as Holtzapple showed that periodic paralysis brought on late in life a slow and gradual deterioration of the muscles chiefly affected.

I believe that the essential condition underlying this disease is congenital defect of metabolism. Other conditions in which we find periodic attacks due to some congenital fault of metabolism are those which are characterized by the excretion of large quantities of (1) acetone and diacetic acid (2) uric acid; and (3) oxalates respectively.

(1) The cyclical vomiting of children associated with acetonæmia, though not common, is sufficiently well known. The attacks, which seem to be due to imperfect metabolism of fatty foods, come on at more or less definite intervals, but are liable to be excited at any time by rich

food, over-exertion, over-excitement, and especially by any combination of these three causes. Here, again, it would seem that the products of imperfect metabolism are stored up in the system until a sufficient quantity is accumulated for what we term an explosion; that this explosion may be due to some exciting cause, that at its occurrence the waste products are violently got rid of by vomiting and by the action of the kidneys, and that after an attack the child has gained freedom for a time. Here, again, we find that careful treatment designed to prevent the formation and accumulation of such waste products will, to a very great extent, prevent the attacks.

(2) The "uric-acid storms," to which other children are subject, are somewhat similar. Here, however, curiously enough, the defect seems to be connected with an inherent disability to carry through the metabolism of ordinary quantities of carbohydrate food. These attacks also show the same tendency to periodicity, may similarly be brought on by over-exertion and over-excitement and too much sweet food, and may, to a great extent, be prevented by careful treatment.

(3) Attacks of oxaluria seems to occur more in adolescent and adult life. They occasionally show a similar tendency to periodicity, unless they are prevented by careful treatment, which in this case also is distinctly successful. They certainly seem to be due to some defective metabolism, and though the treatment is mainly diatetic and the causes very often some error of diet, yet an attack is often brought on by some sudden trouble or worry, or excitement which may be supposed to lessen the patient's vital powers.

In May, 1912, Dr. Head suggested to the writer that the disease might be the expression of an anaphylactic reaction to some form of food, such as pork. Though it was certain that on several occasions the eating of pork sausages had preceded the attacks, it was impossible to make sure that this had always been the case or that he had not sometimes eaten them with impunity. As these attacks are not without danger to life, the crucial experiment of feeding him on pork sausages could not be made. He was, however, warned to avoid pork in any form, and since then has been free from attacks. But at the same time, in deference to his wife's opinion, he has avoided beer and cheese, and in accordance with the writer's own theory, has taken mag. sulph. ʒi. in a glass of hot water every morning and a dose of calomel every fortnight. Moreover, in Holtzapple's cases there is no evidence that the attacks were brought on by any special form of diet, and in Buzzard's patients the attacks could be brought on at any time by a little over-exertion.

There are other periodic diseases which show no tendency to be hereditary, and which do not appear as family diseases. The most striking of these is ophthalmoplegic migraine, which in some respects is closely analogous to periodic paralysis and is also a rare disease. These cases are much more closely analogous to periodic paralysis, especially in regard to the following points:—

(1) The attacks are periodic in their occurrence, and tend to appear at more and more diminished intervals.

(2) They are almost invariably associated with headache, often exactly like ordinary migraine.

(3) They are accompanied by a form of paralysis which is quite temporary in its nature, and at first disappears completely between the attacks.

(4) As a consequence of repeated attacks some paresis may persist during the interval, and eventually partial or even total permanent paralysis may supervene. This is exactly what happened in some of Holtzapple's cases of periodic paralysis who lived on into old age, though the onset of permanent paralysis was much slower in these cases than in ophthalmoplegic migraine.

(5) Cases of periodic ophthalmoplegia have been reported in which the paralysis alone occurred, without headache and vomiting.

(6) Ophthalmoplegic migraine, like periodic paralysis, is to a certain extent amenable to treatment. A case in the writer's care was quite free from attacks while under treatment in hospital for some months for an intercurrent affection, and the paresis of the muscles affected, which had persisted between the attacks, almost entirely cleared up. After he returned to his old home conditions, however, the attacks recurred, and soon became as bad as ever.

The writer came to the conclusion that the attacks of periodic paralysis were due to auto-intoxication, the presence of the toxins being due to some congenital defect in metabolism. The reasons which led him to believe this may be briefly enumerated.

(1) The many points of resemblance to other conditions which are undoubtedly due to auto-intoxication.

(2) The sudden onset and the rapid recovery.

(3) The invariable occurrence of the phenomena after sleep, when waste and toxic products may be assumed to accumulate, just at the time that intestinal digestion is taking place.

(4) The fact that the condition might occasionally be walked off.

(5) The symmetrical distribution of the paralysis.

(6) The occurrence of headache, drowsiness, thirst, anorexia, aching of the limbs and sweating during the attacks. These toxic symptoms closely resemble those which obtain in other transitory toxæmias.

(7) The fact that previous attacks of headache, in all probability toxæmia, had been replaced by the attacks of paralysis.

(8) The high specific gravity of the urine passed during the attacks, and the presence in it of small quantities of indican.

(9) The presence of high pulse tension with accentuated aortic second sound and slow pulse in the initial stages, and the cardiac dilatation and vascular dilatation which so rapidly followed.

The facts that in the recent attacks severe bilious vomiting coming on after some time seemed to cause rapid disappearance of the symptoms, and that in one instance a prompt attack of severe vomiting apparently prevented the development of paralysis, also point to the same conclusion.

Having been led to this belief the writer hoped that treatment adapted to meet this condition of auto-intoxication, and if possible to prevent it, would do good.

The treatment he prescribed was :—(1) The patient was to give up drinking beer altogether, and to avoid all rich food; and he was to drink large quantities of water. (2) To take mag. sulph. ʒi in half a pint of hot water on rising every morning. (3) To take pil. hydrarg. subchlor. gr.ii once a fortnight at bed time, followed by Epsom salts in the morning. (4) To take tinc. digitalis ♏iv ; pot. acetatis gr.xx ; syr. ʒss ; aq. menth. pip. ℥i. Ter. die.[1] (5) To take : Caffein citratis gr.viiss. ; pot. brom., gr.x ; acid hydrobrom. dil. ♏xv; syrup, ʒss. ; aq. chlor. ℥ss.,[2] in a tumblerful of water whenever any warning symptoms of an attack make their appearance.

The success of treatment exceeded the writer's utmost hopes. The attacks, which had been getting more and more frequent, and threatened to incapacitate the patient, at once ceased. It was two years before he had another attack; once or twice warning symptoms occurred, but a dose of the caffein mixture proved sufficient to avert it. Then came the attack after a hard game of football. The patient was told to take his calomel pills and a dose of his caffein mixture, and to eat a light supper and drink no beer and much water after a football match in the future. As long as he did this he played football matches with impunity. Then without the writer's wish or consent came what we may consider the control experiment. The patient discontinued all treatment and drank beer again. The attacks recurred, and threatened to become more frequent. If the hypothesis of an underlying congenital fault of metabolism is the correct one, then we would expect them to recur on the resumption of the patient's old conditions of life; and this is what actually did happen.

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[1] For this prescription the writer is indebted to Singer, who found it very beneficial in his case. Its action was probably purely diuretic.

[2] The bromides in this prescription were inserted in deference to Holtzapple's experience, for he had found them useful in his cases. He also gave caffein, but only in one or two-grain doses. In the writer's opinion it was probably the large dose of caffein acting as a prompt diuretic and cardiac stimulant that was so useful in his case. The bromides were probably useful in preventing sleeplessness and other ill effects from the caffein.

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PUBLICATIONS RECENTLY RECEIVED.

[*Notes on a book under this heading do not preclude a subsequent review.*]

Einführung in die Lehre vom Bau und den Verrichtungen des Nervensystems. Von Professor LUDWIG EDINGER. Zweite vermehrte und verbesserte Auflage. S. 234, mit 176 Abbildungen. Leipzig: F. C. W. Vogel, 1912.

The second edition of Professor Edinger's introduction to the "Anatomy and Structure of the Nervous System" has been enlarged by nearly 50 pages and contains several new illustrations. The general scheme remains the same, but more space is devoted to the sympathetic system and its central connexions, and to a short, but comprehensive, review of the mode of activity of the central nervous system as a whole. The author's aim has been to provide a concise textbook for students and practitioners and to offer them a volume that contains such anatomical facts as are necessary to understand the structure of the central nervous system and the symptoms that organic lesions of different portions of it must produce. But his chapters are not limited to anatomy; where possible he deals not only with the structure of the nervous system, but also with its functions; he treats it not as a piece of complicated organic machinery, but as an active working machine. And short though the book may be, it can be confidently asserted that the student will rise from its perusal with a completer knowledge of what the nervous system is, and how it works than he will probably gain from any other book of the same size. Edinger's own epigram, that anatomy divorced from function is at the best a sterile science, perhaps best indicates the lines on which his book is written.

At the end of each chapter, on each of the main subdivisions of the central nervous system, a short reference is made to the chief symptoms that result from lesions of it; to the neurologist these pages may seem the least satisfactory in the book, but the student will undoubtedly find them useful.

There is certainly no other volume of its size that can be so strongly recommended to the student who wishes to gain an intelligent idea of the structure of the nervous system.

The Theory of Schizophrenic Negativism. By Professor E. BLEULER [Zürich]. Translated by WILLIAM A. WHITE, M.D. Pp. 36. New York: Journal of Nervous and Mental Diseases Publishing Company, 1912.

In this brilliant essay Bleuler concentrated the essential part of his views on negativism, and we are glad to see an English translation for the sake of those who cannot face the difficulties of the original. He makes a serious attempt to explain on psychological lines the negativism which appears in such diseases as dementia præcox and allied conditions, and shows how all theories of motor insufficiency fail to explain catalonic tone and want of action. Negativism is a psychical phenomenon and its expressions are governed by ideas and not by anatomical conditions. The author points out that it often protects the patient, living in a world of subjective ideas and wishes, from the interruption of an unsympathetic environment. It is a general experience that everything which touches a deep complex is at once answered in the negative, for there is an instinctive tendency to conceal it. From the standpoint of these patients the environment is directly inimical and they answer with some negativistic action. The author believes that normal persons allow the pro and con of every action to appear together as a physicist works with two forces in opposite directions; but in these patients mental processes are dissociated and can act unopposed. An external stimulus can call up the one as easily as the other. Schizophrenic patients, like children, swing from one extreme to the other. All who are interested in the modern tendencies in psychiatry should read this remarkable essay.

Die Migräne. Von EDWARD FLATAU. S. 253 with one figure and one coloured plate. Berlin: Julius Springer, 1912.

This is an excellent compendium and review of the whole subject of migraine. After a short historical introduction the etiology and symptomatology of migraine are considered in full detail, and the various hypotheses that have been put forward to explain its nature and origin are then dealt with. Flatau's own conclusion is that migraine is not a pathological entity but a group of symptoms due to disturbed neurometabolic processes. The ductless glands are probably largely at fault, but the immediate cause of an attack is to be sought probably in a local angioneurotic condition of the brain due to a spasm of the vessels.

Die Ulnaris-Lähmung; Monographische Studie als Beitrag zur Klinik der peripherischen Nerven-Erkrankungen. Von Dr. KURT SINGER. Mit einem Vorwort von Geh. Med.-Rat Professor Dr. ZIEHEN. S. 130. Berlin: Karger, 1912.

This work is founded on the author's experience of 44 cases of injury or disease of the ulnar nerve to which he has added a large number taken from the literature of the subject. Almost every known lesion of the nerve is dealt with and authorities are correctly cited. The cases are given with sufficient detail for practical purposes, but the reports are too short to add to our knowledge of the scientific problems raised by the lesions of such a nerve as the ulnar.

Die Psychopathischen Konstitutionen und ihre Sociologische Bedeutung. Von Dr. med. HELENEFRIEDERIKE STELZNER. S. 249. Berlin: Karger, 1911.

The author of this work is a school doctor, medical adviser to a rescue home and to the Courts of Justice for Children in Berlin. Stimulated by Geheimrat Ziehen, she has utilised her material for this study of infantile criminality. Most German alienists teach that grossly immoral tendencies in children depend on mental defects, and many instances in support of this contention are given in this book. Heredity plays a great part, but it is an heredity of weak-mindedness and not of vice. On such weak-minded children vicious surroundings act with redoubled force and they take every opportunity to satisfy their unstable longings, vagabond tendencies and premature sexual desires. This interesting book concludes with an account of the efforts made in Germany to deal with a fundamental difficulty in modern civilization.

Cerebellar Functions. By Dr. André-Thomas [Paris]. Translated by W. CONYERS HERRING, M.D. Pp. 223 with 89 figures in the text. New York: Journal of Nervous and Mental Diseases Publishing Company, 1912.

This is a good translation of the work by Dr. André-Thomas reviewed in BRAIN, vol. xxxv, Part 1, p. 59. It will be useful to those who are not familiar with the French original.

The History of the Prison Psychoses. By Drs. PAUL NITSCHE [Dresden] and KARL WILMANNS [Heidelberg]. Authorized translation by FRANCIS M. BARNES, jnr., M.D., and BERNARD GLUECK, M.D., with an Introduction by WILLIAM W. WHITE, M.D. Pp. 84. New York: Journal of Nervous and Mental Diseases Publishing Company, 1912.

Among the many problems which civilization must face none is of greater importance to society than that of the criminal. In Germany the mental condition of prisoners has long been studied alongside the psychoses of the non-criminal classes. The authors of this work detail in order the work that has been done since 1842, and divide their account into three periods. The first period extended from Delbrück in 1853 to 1890, when Kraepelin's influence began to tell on the study; it was occupied by many works mainly descriptive of the effects produced by imprisonment on the mind of apparently normal individuals.

In the second period, the teaching of Kraepelin led to a more careful correlation of the psychoses with those mental states which occurred in the community at large. Then the third period was reached in which observers were able to separate out those psychoses due to the environment acting on certain predispositions from those which would have been liable to arise in any case. Of the true prison psychoses the majority, 49 per cent., belonged to dementia præcox.

The book contains much information on the dream states into which normal prisoners are liable to fall before they are actually convicted and on the late psychoses of those condemned to long sentences.

Mental Mechanisms. By WILLIAM A. WHITE, M.D. Pp. 151. New York: Journal of Nervous and Mental Diseases Publishing Company, 1911.

This book is in reality a series of papers on current psychological questions so combined that they form a coherent whole. The first chapters deal with the constitution of consciousness with types of reaction and the content of consciousness. Then follows an account of the "complex" and current conception of hysteria with a description of the theory of psycho-analysis. At the end comes a short chapter on preventive principles in mental medicine.

Bibliographie der Neurologie und Psychiatrie für das Jahr 1910. herausgegeben von der Redaktion der Zeitschrift für die gesamte Neurologie und Psychiatrie. S. 202. Berlin: Julius Springer, 1911.

Contains a list of the chief neurological and psychiatrical papers published in the year 1910, and arranged more or less according to the chief subject with which each deals. It seems to be limited to papers reviewed or abstracted in the *Zeitschrift für die gesamte Neurologie und Psychiatrie.* The volume and page of this journal in which the abstract appeared is also indicated. The bibliography will be therefore useful chiefly to those who possess the complete volumes of this journal.

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EDITOR.

[MAY, 1913.]

BRAIN.

PART IV., VOL. 35.

Original Articles and Clinical Cases.

THE ENDOGENOUS FIBRES OF THE HUMAN SPINAL CORD (FROM THE EXAMINATION OF ACUTE POLIOMYELITIS).

BY F. E. BATTEN, M.D.
AND
GORDON HOLMES, M.D.

THE origin, course and destination of the fibres of the spinal cord which connect its neighbouring or more remote segments with one another (internuncial), or pass from one side to the other (commissural), have been extensively studied by experiments on animals, either by following their degeneration after the local destruction of the grey matter from which they arise, or by the method of successive degeneration which was introduced by Sherrington. It is probably the latter method that has given the most complete and accurate results as far as the descending spinal fibres are concerned; for by it the propriospinal fibres can be easily separated from those that descend from higher levels of the nervous system. As other methods, however, it fails to distinguish ascending fibres which terminate, as well as take origin in the cord, from those that pass into the brain-stem.

The methods of secondary degeneration after local destruction of the grey matter that have been employed depend largely on the now well recognized fact that grey and white matter are unequally vulnerable to various noxious influences, and especially to anæmia, and that extensive necrosis of the former may be produced without the destruction of the medullated fibres that pass through the injured region. Thus Ehrlich and Brieger and the many who repeated their experiments were able, by compressing for a time the abdominal aorta of the rabbit, to obtain complete anæmic necrosis of the grey matter of the sacral and lumbar segments of the cord without any degeneration of the medullated fibres that pass through them. This experiment is possible, however, only in rabbits, and it is only in the lower segments of the cord that the destruction can be thus produced, but it has given valuable anatomical information on the course of the fibres that spring from these segments.

Münzer and Wiener have produced similar lesions in rabbits and dogs by the injection of normal sterile saline solution, but though the mechanical effects of this local injection fall chiefly on the grey matter, certain fibres of the white columns may be destroyed or injured by the insertion of the injection needle. Finally, Lamy, and later Rothmann and others, have attempted to determine the course and arrangements of the propriospinal fibres by producing local necrosis in the grey matter of the cord by the injection of granular substances, such as lycopodium powder, into the spinal arteries; but fibres of the white columns were frequently injured by this method.

Anything we know of the endogenous and the propriospinal fibres of the human cord is deduced from our knowledge obtained by these experiments on animals, or by the process of exclusion, as the course of the longer spinal systems is now fairly accurately known. Any direct observations, therefore, that can confirm or amplify these indirectly obtained conclusions must be valuable and desirable.

In acute poliomyelitis we have a disease which, though rarely limited to the grey matter of the cord, produces its destructive effects chiefly in it, and rarely interrupts or produces directly secondary degeneration of the fibres of the white columns. Further, we know that in the severer cases at least the destructive process is not limited to the ventral horns, as the title poliomyelitis anterior acuta suggests, but may, and frequently does, involve the intermediate grey matter and the dorsal horns. Finally, though the lesions are, as a rule, diffuse and widespread in the fatal cases, small and isolated foci of disease may be usually found in certain regions. Consequently by the histological examination by Marchi's method of a sufficient number of recent and suitable cases, it should be possible to determine the distribution and destination of the endogenous spinal fibres that take origin from the affected portions of the grey matter of the spinal cord, the regions in the cross section of the cord that the endogenous fibres as a whole occupy, and those tracts in the cord that contain no endogenous fibres.

Owing to the diffuse and widespread nature of the primary lesions these cases cannot be of much value in settling many anatomical points, and we employ them to throw light on points on which we have otherwise obtained little direct information.

We have been able as yet to examine by Marchi's method only three suitable cases, but the anatomical facts that their study has brought out seem sufficiently interesting to warrant their publication, especially as hitherto a similar systematic examination has been made only by Bing in a single case. Further, while some of our positive conclusions are beyond doubt, the disease was sufficiently extensive in our cases to justify certain negative statements.

All these patients died in the Hospital for Sick Children, Great Ormond Street, under the care of one of us (F. E. B.). The following short *résumés* contain sufficient details of their clinical histories:—

Case 1.—W. B., aged 7, became ill with fever and headache on August 17, 1905; two days later it was found that he lost power in his legs, and on August 22 he was admitted to hospital. Then the flaccid paralysis was limited to his legs, but on September 20 he became drowsy, developed incontinence of urine and fæces, and respiratory difficulty, and eventually he died on September 28, six weeks after the onset of the disease.

On examination there was found very extensive destruction of the grey matter of the lumbo-sacral enlargement and of the lower dorsal region, and similar but more recent lesions were found in the cervical enlargement.

Case 2.—R. A., aged 10 months, was taken ill on October 14, 1909, but weakness was noticed only two days later. On October 17 she could not hold up her head or even cry, and when she was admitted to hospital five days later there was almost complete paralysis of the legs and of the left arm, as well as of the abdominal and thoracic muscles. She developed broncho-pneumonia and died on November 16, a month after the onset of the paralysis.

In this case there was extensive destruction of the grey matter, especially in the lumbar and dorsal segments, but it extended as far caudalwards as the third sacral segment and into the highest cervical region. Deiters' nucleus was also involved on both sides, but no other destructive foci were detected in the brain-stem.

Case 3.—S. C., aged 1 year and 9 months, became ill on November 19, 1909, and was unable to stand on the following day; the right arm was also affected and he was unable to hold his head up. When admitted to hospital fourteen days later he had flaccid paralysis of his left leg, but his right leg, his arms and the muscles of his trunk had partially recovered. On December 19, however, he developed diphtheria and died from diphtheritic paralysis two and a half months after the onset of the paralysis.

There was considerable destruction in the ventral horns of the lumbar segments, and a less severe affection in the cervical region. The disease was, however, not extensive and involved the dorsal horns only in the lumbar segments. There were no lesions in the brain-stem. The Marchi method showed fine granular degeneration in the dorsal roots, especially in those of the lumbo-sacral enlargement, but it could not be traced as a true secondary degeneration up the dorsal columns. It had the histological characters of the fatty degenerative changes found in these medullated fibres in toxic states, and is to be undoubtedly attributed to the diphtheritic intoxication.

In all these cases the microscopical changes were characteristic of acute poliomyelitis, and these are now so well known as not to require further description.

In each of the cases several segments were examined by Marchi's method, while certain regions were cut in serial sections. The brain-stems were also cut serially; in Case 2 these sections extended to the middle third of the optic thalamus, but in Case 1 the brain was not examined above the anterior quadrigeminal bodies, and in Case 3 only to the posterior quadrigeminal region. As practically the same changes were found in all cases, they may be described together.

SPINAL CORD.

The most prominent change visible in Marchi preparations in the segments in which there was extensive destruction of the grey matter was degeneration of the ventral spinal roots (figs. 1 and 2); these degenerated fibres could be frequently followed from various portions of the ventral horns through the ventral columns, but neither their arrangement nor course presented features worthy of special mention. In regions where the disease was unilateral there was no evidence of root-fibres taking origin in one ventral horn and after decussation passing into the opposite ventral roots.

In two of our cases, however, we had an exceptional opportunity of observing the origin and the course of the fibres of the spinal portion of the spinal accessory nerve, as these fibres were degenerated and were consequently easily traced by Marchi's method. The nucleus of origin and the intramedullary portions of the fibres could be followed through the upper six cervical segments. In the lower segments,

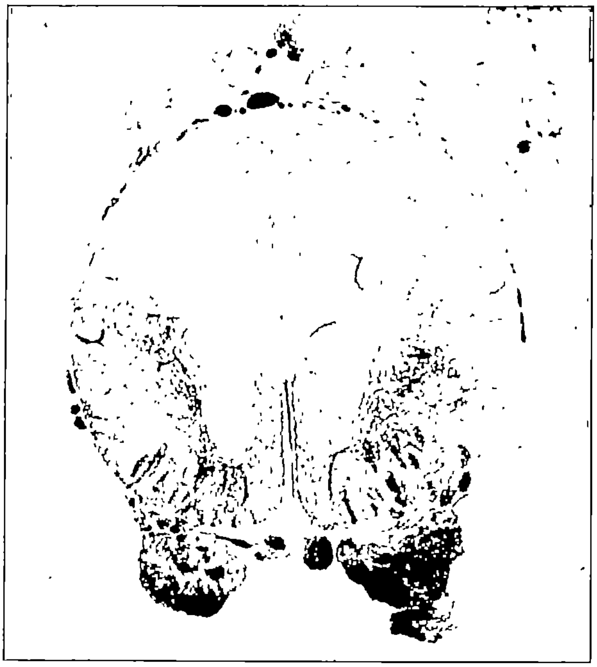

Fig. 1.

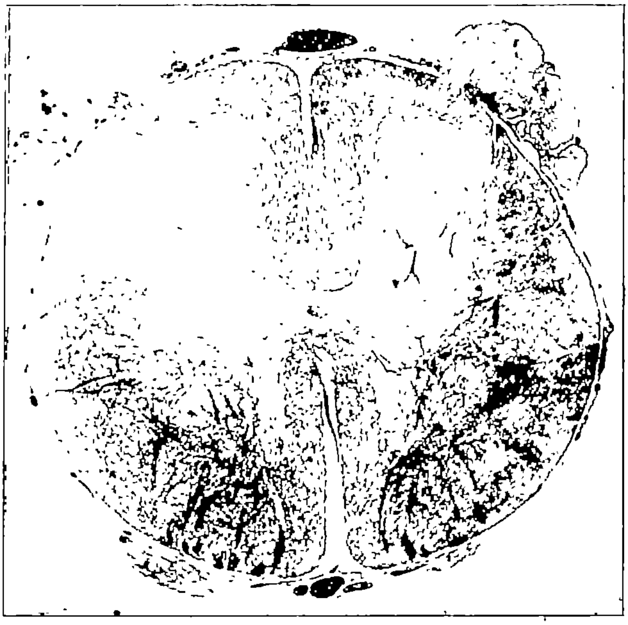

Fig. 2.

Photographs of Marchi preparations of the second sacral and third lumbar segments of the spinal cord to show the extensive destruction of grey matter, and the secondary degeneration that has resulted from it.

the sixth, fifth, and fourth, these root-fibres could be traced from a group of cells lying in the ventrolateral part of the ventral horn (fig. 7), and from it they passed horizontally, or slightly obliquely dorsalwards, to the base of the dorsal horn, where some of them bend cerebralwards to form a compact bundle, or a group of smaller bundles, which could be traced to the upper end of the spinal cord (fig. 8); they are easily recognizable in normal specimens. In the lower segments in which they are found, these transversely cut fibres lie embedded in the neck of the dorsal horn, while in the higher cervical segments some occupy the inner part of the formatio reticularis of the lateral column (fig. 8). But at certain levels along its course certain fibres pass from this intramedullary bundle horizontally, or somewhat obliquely upwards, through the lateral columns to form the extramedullary portion of the root. In the lower segments these fibres generally run along the lateral border of the dorsal horns (fig. 7), but in the higher many

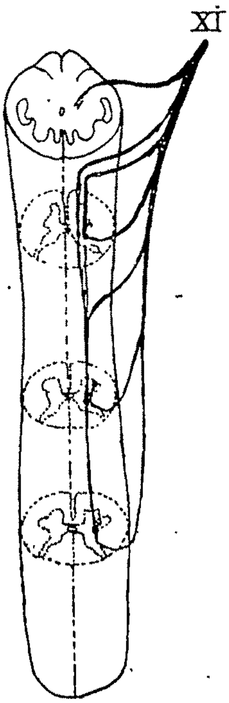

FIG. 3.

Diagram of the course of the root-fibres of the spinal portion of the spinal accessory nerve.

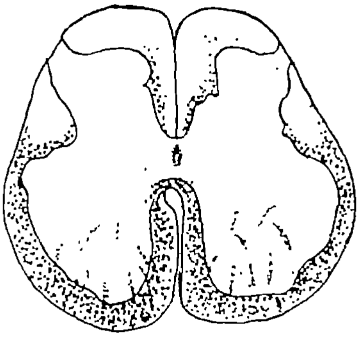

FIG. 4.

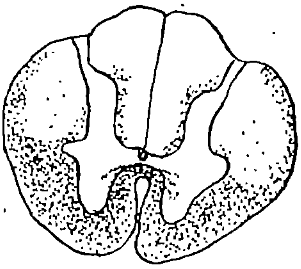

FIG. 5.

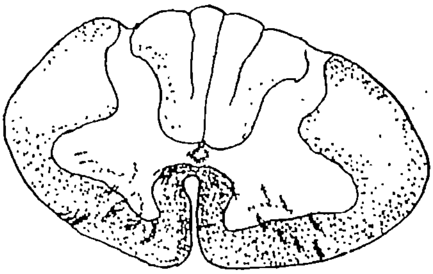

FIG. 6.

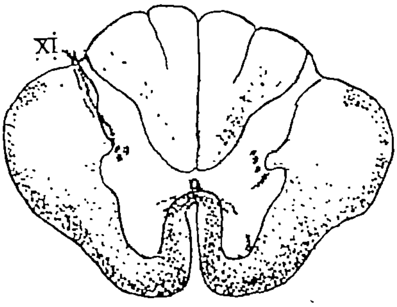

FIG. 7.

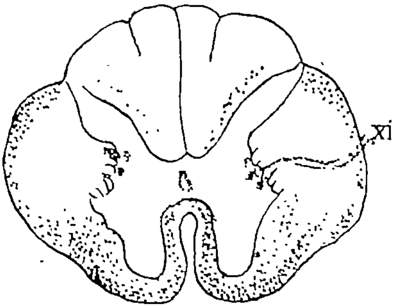

FIG. 8.

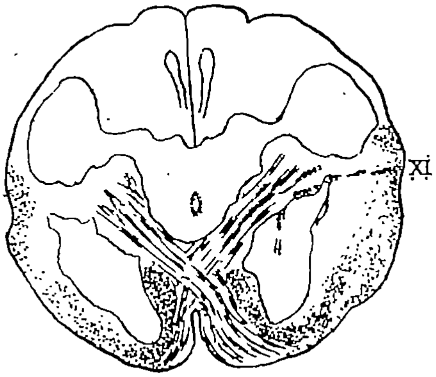

FIG. 9.

Drawings from Marchi preparations of the position of the degenerated fibres in different segments of the spinal cord.

pass directly lateralwards through the lateral columns as Kölliker has described (figs. 8 and 9); but root-fibres passing in both directions were occasionally present in the same section. We could, however, trace some fibres directly from their nucleus of origin to the periphery of the cord, unconnected with the intramedullary bundle.

Towards the upper end of the spinal cord this intramedullary bundle disappears owing to its fibres passing outwards to join the rest of the root, but some of its fibres could be traced as high as the decussation of the pyramids (fig. 9). Thus the root-fibres of the spinal accessory nerve run cranialwards in two parallel bundles, the one intra- the other extra-medullary, which are connected at short intervals by fibres passing from the former to the latter (fig. 3). It is always difficult to determine accurately in Marchi preparations the exact origin of root-fibres, but our observations conform with those of Bunzl-Federn and Sano, who found the lower fibres connected with cells in the ventrolateral part of the ventral horn, and some of the higher coming from a group more in the centre of the horn. Roller recognized that certain of the root-fibres of the spinal accessory nerve take a longitudinal course within the spinal cord before their exit, and Darkschewitsch has described this more fully by studying their myelinization in human fœtuses. He noted too that the apparent origin of the root-fibres from the middle cervical segments may vary, as the proportion of fibres that ascend in the spinal cord before their exit is not constant. Van Gehuchten has discovered an exactly similar course of the root-fibres in lower mammals (rabbit) as that which we describe in man by tracing their retrograde degeneration after the main root had been torn out at the side of the bulb; and Cajal has, by the aid of Golgi's method, made out the same course in the cat and rabbit.

The ventrolateral columns of each cord contained a large number of degenerated fibres; the majority of these ran longitudinally, but some could be traced into the ventral commissure. They were most numerous in the segments in which the grey matter was most severely involved and gradually diminished in number as they were traced into segments in which there was less disease. In every instance the degenerated fibres were densest in the ventral columns, ventral and ventrolateral to the ventral horn; in the sacral and lumbar segments, which were generally most affected by the disease, these regions were diffusely strewn with granules stained black by osmic acid (fig. 4). They were always most closely packed in the immediate neighbourhood of the affected grey matter, while in regions in which there was less inflammatory change, as in the higher cervical and in some of the dorsal segments (figs. 7 and 8), they were separated from it by a zone of normal fibres. The majority of these degenerated fibres are internuncial, and their arrangement evidently depended on the law that the longer fibres lie more peripherally in the cord, while the shorter, that connect only adjacent segments, remain close to the grey matter.

In the severely affected regions of the cord, where the degenerated fibres were scattered diffusely throughout the ventrolateral columns, no definite systematization could be recognized, but in the less involved regions the longer fibres ascending from the more caudal segments to the upper portion of the cord or to the brain-stem, could be distinguished on the periphery of the ventral columns. The most dorsal of these fibres spread into the lateral columns, and in the higher cervical segments were separated from the periphery by the ventral borders of the ventral spinocerebellar tracts (figs. 8 and 9).

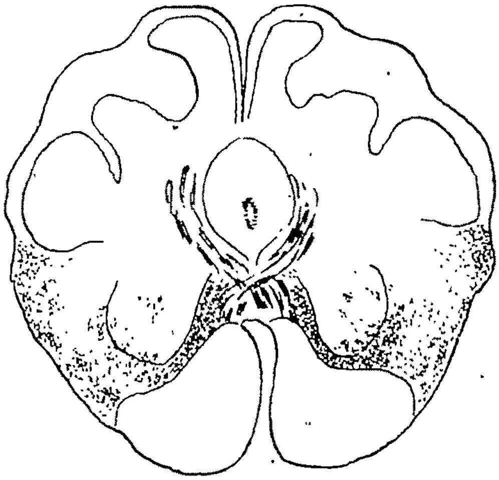

FIG. 10.

It was impossible to distinguish ascending and descending fibres in degeneration except in regions in which there was little primary disease, or above or below its level. In one case in which the sacral segments were almost spared the extensive degeneration they contained was evidently predominantly descending, while that found in the higher segments when these escaped was ascending. Evidently large numbers of both ascending and descending propriospinal fibres exist.

In two of the cases the degenerated fibres were displaced lateralwards from the ventral fissure in the upper half of the cord by the presence of a large direct ventral corticospinal tract.

In the three cases there was also bilateral degeneration of the spino-cerebellar tracts which we could follow from the lower dorsal segments of the cord to their termination in the cerebellum; the ventral and dorsal tracts were about equally affected. The existence of the diffuse degeneration in the lateral columns already described made our material unsuitable for the accurate investigation of the relations of these tracts in the spinal cord, but they were easily identified where they separated from the spinal fibres in the medulla oblongata and in the cerebellum (figs. 11 and 12).

The region of the ventrolateral column which in all our cases contained least degenerated fibres was that occupied by the crossed pyramidal tracts, in which at the most only a few isolated fibres were affected, and in the white matter immediately on the lateral border of the dorsal horns. This latter would correspond to Bechterew's "median bundle"; it was only in the immediate neighbourhood of severely affected grey matter that this region contained any considerable number of degenerated fibres.

Commissural fibres.—In addition to the longitudinal fibres of the cord, many of those of the ventral white commissure were degenerated, but only at or near those levels where the grey matter was involved. Frequently these degenerated fibres could be traced from one ventral horn through the commissure into the opposite ventral column, in which they appeared to become oblique.

Dorsal columns.—The state of the dorsal columns of the cord in acute poliomyelitis, which it is now recognized produces foci of degeneration in all parts of the grey matter, is of special interest, as it may throw light on the vexed question of the distribution of the endogenous spinal fibres that these columns contain. Considering the frequency of dorsal root degeneration in toxic and acute infective states, it was surprising that in only one of our cases was there any noteworthy affection of these fibres.

In all the cases the dorsal columns were freer from degeneration than any other region of the cross section of the cord; in none of them could any ascending degeneration be detected in Goll's columns in the cervical region, and the longer descending tracts—Schultze's comma, Hoche's peripheral bundle, Flechsig's oval field, and Gombault and Philippe's triangle, contained not a single degenerated fibre. Marchi preparations showed only diffusely scattered granules near the grey

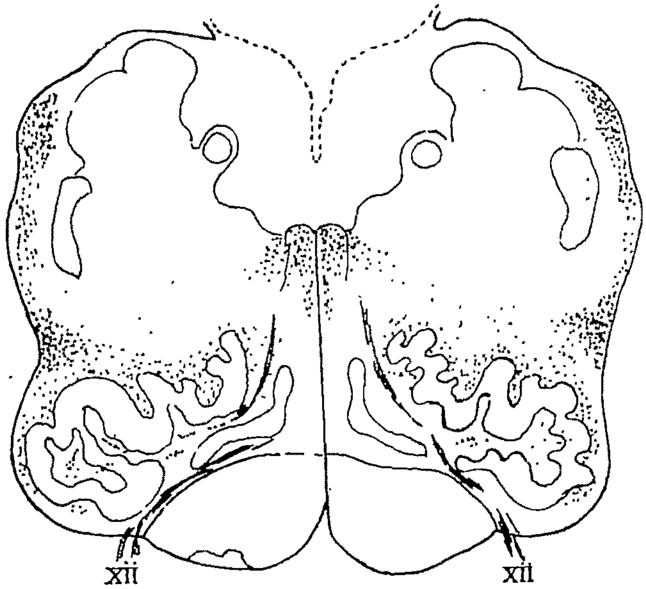

FIG. 11.

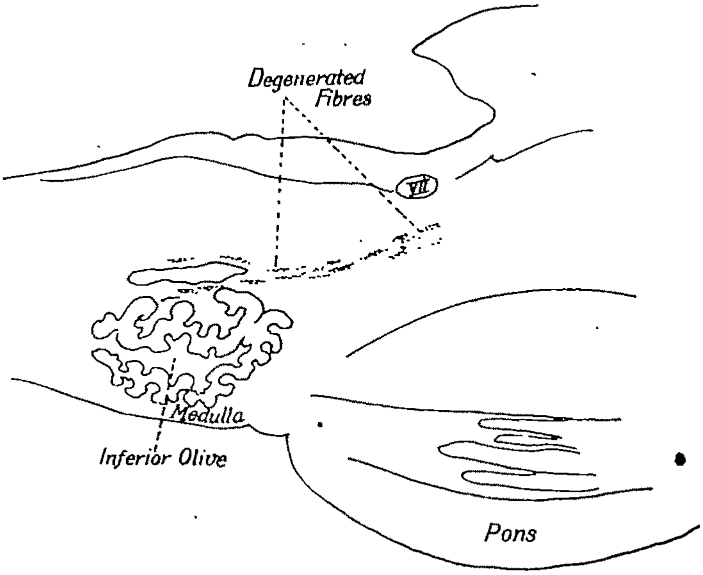

FIG. 12.

Longitudinal sagittal section of the medulla oblongata in the plane of the dorsal vagus nucleus.

matter along the ventral half of the dorsal horns, and especially in the cornu-commissural angle. In these regions the amount of degeneration corresponded roughly with the amount of local disease in the grey matter (figs. 4 and 5).

This complete absence of degeneration in the longer ascending and descending tracts of the dorsal columns is strong evidence that these regions contain only exogenous or radicular fibres. Whether the descending tracts are composed wholly of radicular fibres has been for long a much debated question. Early observers, as Tooth and Marie, together with Schaffer, Nageotte, and Gombault and Philippe, came to the conclusion that they are chiefly endogenous; while Schultze, Redlich, Zappert, and Goldstein believed they are wholly exogenous. Others, as Dejerine and Spiller, Marburg, Wallenburg, and Bruce, assert that these descending systems contain both endogenous and exogenous fibres. Collier and Buzzard, Homén and others have demonstrated exogenous fibres within them, but are not certain if they contain propriospinal fibres as well. The complete absence of degeneration in them in our cases necessitates the alternative conclusions that either their fibres are wholly exogenous, or that the portions of grey matter from which they take origin escaped completely. The latter alternative is extremely improbable in view of the wide distribution of the disease. Further, in Bing's case of acute poliomyelitis also these columns contained no affected fibres, and the only degeneration in the dorsal columns was of the same distribution as we describe. Finally, these tracts have not been found to be degenerated in animals in which the grey matter of the cord was destroyed by cutting off its blood supply (Ehrlich and Brieger), by embolism of the spinal arteries (Rothmann), or mechanically (Münzer and Wiener). It is true that these experiments were carried out chiefly on the lower mammals, but the dorsal columns of these animals apparently contain long descending fibres similar in distribution to those that exist in the higher mammals. We must therefore accept the conclusion that the system of descending fibres contained in Schultze's comma, Hoche's bundle, Flechsig's oval field, and Gombault and Philippe's triangle are wholly of exogenous or root origin. We also failed to find the long ascending endogenous fibres running near the septum that have been described by Münzer and Wiener, and by Rothmann in lower mammals. In man at least the endogenous fibres of the dorsal columns lie in the zone adjacent to the ventral half or two-thirds of the dorsal horns and in the cornu-commissural region, and seem to have a short course only.

Brain-stem.—The degenerated fibres that pass cerebralwards from the spinal cord were easily traced to their termination in the serial sections; this was especially so in Case 3, in which the brain-stem was divided by a mesial incision and the one-half cut in the sagittal, the other in the horizontal plane. Unhappily in Case 2 inflammatory foci had destroyed Deiters' nuclei on both sides and produced degeneration of the fibres that take origin in them (fig. 13); but recognizing this it was easy to distinguish the degenerated spinal fibres, especially by correlating the findings with those in the other two cases.

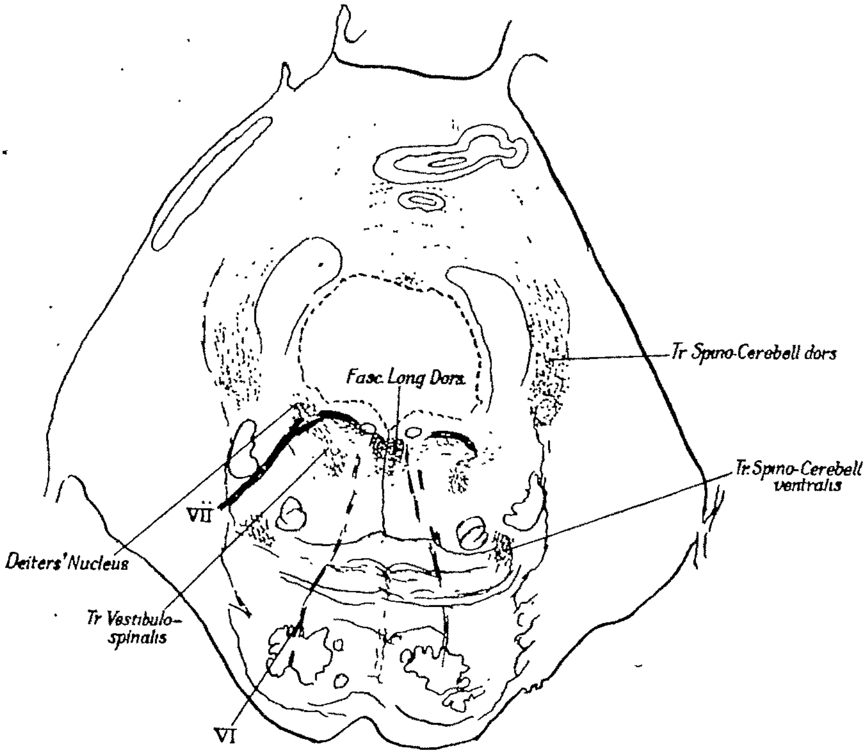

FIG. 13.

Transverse section of the pons varolii and cerebellum to show the degeneration resulting from local lesions in Deiters' nuclei, and the degeneration ascending from the spinal cord in the spinocerebellar tracts and the dorsal longitudinal bundles.

As the upper cervical segments were little affected in our cases, the degenerated fibres that passed through them from lower segments of the cord were arranged mainly in the periphery of the ventral columns and in the spinocerebellar tracts. The latter were followed to the vermis of the cerebellum, but we have nothing new to add on either their course or destination.

The degenerated fibres of the ventrolateral columns maintain the same relative position around the ventral horns till these disappear, lying close to them on the mesial side but separated from them laterally by a relatively normal zone (fig. 9). They are, however, displaced lateralwards and dorsalwards from the ventral fissure by the corticospinal tracts when these attain their ventral position in the pyramids (fig. 10). At the lower end of the inferior olives these degenerated fibres, which to this level had lain as a crescentric band around the ventral horns, divided into two groups between which only sparse and irregularly arranged fibres were found (fig. 11). The one group lay around the inferior olives, chiefly dorsolateral to them, and between them and the dorsal accessory olives; the other group passed into the dorsomedian portion of the cross-section of the medulla, and its fibres entered the dorsal longitudinal bundle, or ran ventral to this on the side of the raphe, but a certain number remained scattered in the adjacent parts of the formatio reticularis (fig. 11).

The fibres of the ventrolateral group diminished rapidly in number as the olives increased in size; their destinations, as far as could be determined in Marchi preparations, were: (1) In the inferior olives and probably in the dorsal accessory olives. Many fibres could be seen to bend transversely, pierce the myelinated capsule of the olive and enter its grey matter; while other degenerated fibres seemed to enter the hilum of the olives and reach its grey matter from within. The greater number of these fibres terminated in the lower third of the olives, but a few could be followed to its oral half. (2) Other fibres that lie dorsal and dorsolateral to the inferior olives are not sharply separable from the spinocerebellar tracts in the lower part of the medulla; these seem to end gradually in the ventral portion of the formatio reticularis, but a considerable number pass through the nuclei laterales medullæ and some probably terminated in them. (3) A small bundle of degenerated fibres, which was first traced in the sagittal and horizontal series and was later identified in one of the transverse series, passed off from those that surround the inferior olives at about the middle third of the latter, obliquely cerebralwards and dorsalwards through the formatio reticularis, approximately in the plane of the dorsal vagus nucleus. They could be traced between the roots of the sixth and seventh nerves, and seemed to end in the grey matter that lies here in the dorsal half of the formatio reticularis, and perhaps in the nucleus centralis inferior (fig. 12). These are the destinations, as far as they could be ascertained in Marchi sections, of the fibres of the ventrolateral group. They have all, with the exception of the third bundle, ended at about the upper third of the medulla oblongata, or at least at the lower margin of the pons.

The dorsomesial group could be traced further cerebralwards, but at about the middle of the medulla oblongata those fibres contained in the formatio reticularis began to disappear rapidly, terminating apparently in its grey matter. In one of the cases a few fibres could be followed immediately under the grey matter of the fourth ventricle and aqueduct, lateral to the dorsal longitudinal bundle, throughout the pons and midbrain into the caudal portion of the optic thalamus; in the upper part of the midbrain, these fibres, which were few in number, lay on the mesial side of Forel's bundle, while they entered the thalamus in the dorsomesial portion of Forel's field. As far as we could trace them they seemed continuous with the fibres of the ventrolateral column of the cord, but in the case in which we found them there were symmetrical lesions in Deiters' nuclei, but no other foci of disease that we could discover in the brain-stem. The degenerated fibres in the dorsal longitudinal bundles diminished in number rapidly at the lower end of the pons, especially at about the level of the sixth nerve nuclei, but some could be traced into the midbrain.

The anatomical significance of the degenerations found in the spinal cord, and especially those in the dorsal columns, has been already discussed, and some reference may be now made to those fibres of spinal origin which we have traced into the brain-stem. Excepting the spinocerebellar tracts the most prominent of these were those ascending from the ventrolateral columns that terminate in the inferior olives and their accessory nuclei. These fibres have been described by Bechterew, Dydynski, Collier and Buzzard, and Page May. Our observations agree closely with Dydynski's, as the "Olivenbundel" which he traced in man from the midthoracic region, lay near the exit of the ventral roots, and there was no doubt that it was the more lateral of the spinal fibres that we traced to the olives.

Many authors who have traced by the degeneration methods fibres from the spinal cord into the brain-stem have been struck by the considerable number which apparently terminate in the formatio reticularis; the majority of these end irregularly and cannot be grouped into bundles or definite systems. Sherrington and Cajal have seen some of these fibres enter the nuclei laterales of the medulla. We have not been able to trace any of these fibres of spinal origin directly to the nuclei of the vagus or acusticus nerves, or to Deiters' nucleus as Rothmann has described.

We have been unable to find any previous reference to, or description of, the compact bundle of fibres which we traced in two cases from the ventrolateral columns of the cord, dorsal to the inferior olive, towards the nucleus centralis inferior. In neither of the cases in which we found it were there any local medullary lesions to which the degeneration could be due.

Fibres have been also repeatedly traced from the ventral columns of the cord into the dorsal longitudinal bundles, but they have been rarely followed as high as the midbrain. Rothmann, for instance, saw them disappear in the upper half of the pons, but Collier and Buzzard traced a few as high as the posterior commissure.

The few degenerated fibres we followed through the brain-stem ventral to the central grey matter, lateral to the dorsal longtitudinal bundles, are hitherto undescribed in man, but as in the case in which we found them there were lesions in the brain-stem, *i.e.*, in Deiters' nuclei, we cannot be certain they came from the spinal cord. Lewandowsky describes the fibres of Forel's bundle as extending from the inferior olive through the lateral portion of the formatio reticularis, and this course corresponds closely with that of those fibres we found degenerated in these cases.

CONCLUSIONS.

(1) The spinal portion of the spinal accessory nerve has a large intramedullary root which extends throughout the upper five or six cervical segments of the spinal cord.

(2) The longer descending systems of the dorsal columns—Schultze's comma tract, Hoche's marginal bundle, Flechsig's oval field, and Gombault and Philippe's triangle—do not contain endogenous fibres in man.

(3) The propriospinal fibres of the ventrolateral columns are arranged in man as in other mammals, and conform in their arrangement to the law that the longer fibres lie nearer the surface of the cord.

(4) Many fibres of the ventrolateral columns ascend to the brain-stem and terminate in the inferior olives, in the formatio reticularis bulbæ et pontis, in the nucleus centralis inferior, and probably in the nuclei laterales of the medullæ; others ascend in the dorsal longitudinal bundles as high as the midbrain.

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A CONTRIBUTION TO THE PATHOLOGY OF CHRONIC PROGRESSIVE CHOREA.

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CHRONIC progressive chorea is a curious affection which occurs comparatively late in life, characterized by irregular movements, disturbance of speech, and an accompanying psychical derangement, terminating gradually in dementia. Homogeneous heredity is not always present, although of frequent occurrence.

While it is generally conceded that the disease has no well-founded relation to Sydenham's chorea, and should be regarded as a nosological entity *per se*, some writers (Monnier) still contend[1] that this distinction should not be made.

Much interest lies in the pathology of the disease, but the anatomical lesions found at *post-mortem* vary greatly, making it difficult to judge of their respective values.

Following is a report of the pathological findings in two cases of chronic degenerative chorea. Only a brief *résumé* of the clinical histories will be given.

Case 1.—C. S., male, labourer, admitted November 20, 1907, died January 8, 1913. Concerning the family history of the patient, other than the fact that his father was alcoholic, but little definite information could be obtained. Patient was born in the State of Ohio, in 1841. His early childhood was uneventful; he learned to walk and talk when 1½ years old. Whilst a child he had no convulsions or fits. He began school at the age of 6 years, learned to spell with difficulty, but succeeded fairly well with his studies, and was of a sociable disposition. He enlisted in the Army at 23 years of age, and served two years. His habits were good; no history was obtained of syphilis, sexual excesses, or the abuse of drugs. The onset of his illness was gradual, the first choreic movements being noticed at the age of 52; they gradually increased in severity and extent. When admitted to this hospital, physical examination showed the patient to be of a strong frame, but poorly nourished. The pupils were equal and slightly dilated; accommodation was normal, and direct and consensual reactions for light were unaffected. No pronounced anomalies of the ears were evident, but the palate was high and narrow. Exaggeration of the deep reflexes was evident and of the superficial slight. The chest was well formed and symmetrical. Respiratory organs showed nothing abnormal upon percussion and auscultation. The heart was not obviously enlarged. A slight aortic murmur, however, was perceptible. Pulse 80 per minute, somewhat irregular. Examination of the abdomen and genito-urinary tract was negative. Temperature normal. Integument dry. Hearing, taste and smell normal. Urine: colour pale yellow; acid reaction, specific gravity, 1010; trace of albumen; no casts but a few leucocytes.

Throughout the patient's residence in this hospital his choreic movements were a prominent feature. His gait was erratic and uncertain, and somewhat resembled that of a drunken man. Peculiar gestures, poses and irregular jerking of the muscles were continuously present. They were increased by embarrassment and emotion, but lessened in repose and subsided during sleep. His mental state was that of depression and he gave evidence of a suicidal tendency. He became irritable without appreciable cause, used profane language, and assaulted other patients without provocation. His speech was thickened and drawling in character. He was untidy in his person and dress. Delusions of persecution were evident. His memory was weakened, and judgment and reasoning defective. Progressive mental and physical enfeeblement supervened, and the patient died January 8, 1913, after the disease had lasted for twenty years.

POST-MORTEM RECORD.

External examination.—Body large and well nourished.

Internal examination.—Head: The calvarium was symmetrical, wall thick, diploe compact. Dura, somewhat adhered to skull, thickened. Inner surface smooth. Pia, showed a slight opacity over the convexity of the brain, and the cerebrospinal fluid was slightly increased.

Brain: Weight 1,030 grm. Slight general atrophy was present. No decortication occurred upon removal of the pia. The basal vessels showed but slight sclerosis. The lateral ventricles were not dilated. No granular ependymitis of the lateral or fourth ventricles.

Spinal Cord: Considerable diminution in the size of the spinal cord was evident. Otherwise, no macroscopical lesions could be detected.

Thorax: Pericardium normal. Heart, weight 350 grm. Right auricle enlarged. Tricuspid orifice admits four fingers, valve somewhat thickened. Right ventricular wall thickened, cavity enlarged. Pulmonary valve normal. Left auricle enlarged. Mitral orifice admits three fingers. Mitral valve thickened. Left ventricular wall thickened, cavity dilated. Aortic leaflets thickened and slightly atheromatous.

Lungs, weight 550 grm.—left 510 grm.—slight hypostatic congestion, œdema, and emphysema.

Liver, weight, 1,300 grm. Surface smooth, capsule thickened. Fatty infiltration. Gall-bladder normal. Spleen, weight 150 grm. Capsule thickened, surface smooth, pulp soft and red in colour. Pancreas normal. Stomach and intestines normal.

Genito-urinary tract: Kidneys, weight, right 80 grm., left 130 grm. Left kidney, capsule somewhat adherent, surface granular, cortex narrow and ill-defined. Numerous small cysts present. Pelvic fat increased. Right kidney small, contracted, capsule strips with difficulty, surface irregular, cortex thin. Large cyst in lower portion. Bladder, slight congestion of mucous membrane.

MICROSCOPICAL EXAMINATION.

Numerous pieces from different regions of the brain and spinal cord, together with parts of the radialis, ulnaris, medianus, ischiadicus, and cutaneous femoris posterior nerves were fixed in alcohol, formal, Weigert's mordant, Müller's fluid, Orth's fluid, and special fixing reagents. The following staining methods were utilized: thionin, toluidin blue, cresyl violet, polychrome methylene blue, Van Gieson, Unna-Pappenheim's, Weigert's resorcin-fuchsin, Alzheimer's for glia, Herzheimer's, Bielschowsky's, Weigert's for neuroglia fibres, Weigert's myelin-sheath, Marchi's, Mallory's, Mann's, Heidenhain's, hæmatoxylin, gentian violet, and others.

Precentral gyre: With Van Gieson's stain a diffuse connective tissue thickening of the pia is present, with toluidin blue numerous large fibroblasts are seen which contain a considerable amount of lipoid material within their cytoplasmic processes.

A study of the cellular elements in this area indicate that degenerative changes are evident in the cells throughout, but especially in the deeper layers of the cortex. Only a few of the Betz giant cells, however, show degenerative changes.

The commonest and most extensive change occurring in the degenerated ganglion-cells is that affecting the Nissl substance. A general chromatolysis is frequently seen, not only in the cell body, but extending for some distance into the protoplasmic processes. This consisted in a breaking up of the tigroid substance into small darkly stained granules, distributed more or less regularly throughout the cell body. Around the periphery of the cell bodies, the Nissl corpuscles in some of the cells are fairly well preserved. The nuclei also present some interesting changes. The nuclear membrane is sometimes hardly discernible, and the contour of the nucleus irregular. In some, small blue granules can be seen lying in the nucleoplasm. The nucleus often occupies a position near the periphery of the cell, in some cells staining more deeply than normal, and in other cells vacuolar degeneration is apparent. Many cells show an abnormal increase of lipoid material. This substance appears as irregular masses lying within the meshes of a violet stained, net-like structure into which the entire cytoplasm of some of the cells is converted. In the cells the nuclei are eccentrically located and show pathological changes, and the apical processes present an unusually tortuous aspect.

A more or less general shrinkage characterizes the changes in many cells. The cytoplasm and processes are filled with darkly stained coarse granules. Some are shrunken to such an extent as to present a rod-like appearance. Vacuolar degeneration is present in a few cells; in some cases the vacuoles are large; in other instances the cell body is filled with numerous small vacuoles; the protoplasmic processes have disappeared and the nucleus is deformed and shrunken, and a more or less well-defined pale area is seen surrounding the nucleus. A considerable increase of the chromatin granules within the nucleus can be observed. Sometimes a chromatin network occurs in parts of the nucleus. Not infrequently the nucleus contains small vacuoles, the nucleolus is enlarged, and lies close to the nuclear membrane.

Sclerosis of the ganglion-cells is also evident. When stained with Nissl toluidin blue the nuclei are darkly stained and present a pyramidal shape. The cytoplasm is often so darkly stained in the region of the nucleus that the limits of the latter are quite indistinct. The nucleoli are greatly increased in size. The apical processes are tortuous and can be traced for an unusual distance. The axis cylinder processes are shrunken. The tigroid substance is frequently clumped in masses within the cell body.

In Bielschowsky preparations the entire cell appears more darkly stained than normal. The nucleus presents a triangular shape and is darkly stained. A net-like structure surrounding the lipoid granules is also discernible.

Many cells are swollen and the Nissl substance lightly stained. The nucleus and nucleolus are enlarged and faintly stained. The protoplasmic processes and axis cylinder can be traced for a considerable distance. The cytoplasm is seen to consist of a fine granular structure. These cells are not so deeply stained by the Bielschowsky method as those which have undergone sclerotic changes. The cytoplasm is pale and the neurofibrils scarcely perceptible. The nucleus is large, pale and presents an oval or round form. Groups of small granules are often seen within the nucleus. The nucleolus is enlarged and occupies an eccentric position; sometimes it is darkly stained and in other instances of a light brown colour. Here and there cells are seen in which only a faintly stained ring of cytoplasm remains surrounding the nucleus.

An increase of the glia-cells is readily discerned. This hyperplasia is seen to be most pronounced in the deeper layers. The predominating type is the small non-fibre building glia-cells, having an intense darkly stained nucleus, surrounded by a scanty, somewhat densely stained irregular cell body. Sometimes the cytoplasm is composed of vacuoles or cysts containing masses of fat. This fatty material stains a yellowish, or yellowish-green colour, by toluidin blue and usually lies on one side of the nucleus. The protoplasmic processes are occasionally seen to contain groups of cysts filled with fat granules at some distance from the cell body.

Glia-cells having a large lightly-stained nucleus are seen, but are not so numerous in general as the small glia-cells. The nucleolus is large and is often metachromatically stained, or several nucleoli can be observed lying among the blue stained chromatin granules. The cell body is more or less ill-defined, although more copious than in the smaller cells, and, especially in those cells surrounding degenerated ganglion-cells, is seen to contain numerous lipoid granules; occasionally glia-cells are seen having angular or dumb-bell shaped, small, darkly stained homogeneous nuclei.

The number of glia-cells in the vicinity of ganglion-cells is obviously increased. They generally occupy a position around the base of the cell. Ganglion-cells are not infrequently met with in the lower layers which have become swollen, deformed, and apparently invaded by glia-cells; i.e., a passive neurophagia is present. Sometimes one and occasionally several glia-cells can be found within the cytoplasm of the nerve cell.

A great increase in glia-fibres is perceived in sections stained by Weigert's method for neuroglia. The membrana glia superficialis is greatly thickened, and amyloid bodies are rather numerous. The increase of fibres, however, is most pronounced in the lower layers of the cortex and in the white matter. Some fibres are conspicuous for their thickness and tortuous course. Around the blood-vessels an increase in the number and size of the glia-fibres is seen.

The nuclei of the endothelial cells of the vessels are darkly stained, shrunken, angular, sometimes round and sometimes lightly stained. The cell body of the endothelial cell is sometimes unstained and sometimes has quite a perceptible reticular structure. The meshes of the net-like structure are filled with yellowish and green coloured granules. Sometimes the endothelial cells appear to have completely disintegrated. Frequently the fat granules only lie around the border of the cell, and it seems as if in such instances a fatty infiltration of the cement substance had occurred.

The cells of the muscular coat of the vessels are in many instances degenerated and filled with fat. The adventitial cells are shrunken, darkly stained, and many of them contain products of disintegration, viz., lipoid material and basophilic metachromatic substance. Some of them are filled with unusually large irregular masses of fat, while others contain smaller granules more regular in size and shape.

A thickening and hyperplasia of the adventitial connective tissue, with swelling of the elastica, is evident in some of the vessels. Capillary knots and spiral formations are encountered. The adventitial spaces of many of the vessels, especially in the white matter, contain Körnchen cells filled, as a rule, with dark green coloured pigment.

The changes in the veins are similar to those in the arteries. Many of the adventitial cells are seen to contain greenish and yellowish granules of lipoid material.

By the Weigert-Pal method the cortex shows a rather diffuse falling out of medullated fibres. The supraradiary and tangential are especially sparse, in fact the latter seem to have entirely disappeared in some places. The oblique fibres forming the interradiary plexus are likewise diminished.

Examination of preparations from the post-central and para-central gyri show the pathological changes to be similar to those occurring in the precentral convolution. The alteration in the tangential fibres and the supraradiary plexus, however, appears to be somewhat less pronounced.

First frontal convolution: The pia is thickened and hyperplasia of the connective tissue elements visible.

The greatest alteration in degree and number of ganglion-cells is found in the medium and large-sized pyramids of the ganglionic layer. The small pyramids contain much pigment, and many of them are stained unusually darkly. Some of them show central chromatolytic changes. The nuclei are often elongated, deformed, and occupy an eccentric position. Vacuolar degeneration is present in some instances. Other cells are shrunken and their processes appear separated from the cell body. The large pyramidal cells show similar changes, but to a less degree than the small cells. Cleavage and granular degeneration of the neurofibrils is apparent in the majority of the small cells, but in most of the large pyramids the neurofibrils remain intact.

The membrana glia superficialis is somewhat thickened. A degeneration of the tangential fibres and the supraradiary plexus can be discerned. The radial fibres, however, are but slightly affected.

A marked increase of the glia elements and fibres is visible. The alterations in the glia-cells are analogous to, but somewhat less pronounced than those in the cells of the precentral area. Here also the small type of glia-cells predominates, but cells with large pale nuclei and metachromatically stained nucleoli present a conspicuous feature of the microscopic picture. The walls of some of the vessels are thickened, and their cellular elements shrunken and darkly stained. The adventitial spaces in many instances contain pigment.

Temporal region: The pathological changes in this area correspond to those found in the frontal convolutions, but are less severe in character.

Occipital region: Many of the ganglion-cells are well-preserved, while others are swollen and faintly stained; some are shrunken and darkly stained, and in many cells an abnormal increase of lipoid material is evident. A hyperplasia of the glia is present. The oblique and tangential fibres are somewhat reduced in numbers. The pia is but slightly thickened.

Hippocampal region: The marginal glia is thickened and contains many corpora amylocea. The ganglion-cells are considerably altered. The prevailing type of degeneration is sclerosis of the cells with increase of pigment.

Numerous large glia-cells are seen with thickened fibres, especially in the vicinity of blood-vessels. By Bielschowsky's method a granular fibrolysis is visible in some cells, but neither the fibrillar change of Alzheimer nor senile plaques are present.

The changes in the corpus striatum and optic thalamus are very great. The caudate nucleus appears less affected than the lenticulate nucleus and optic thalamus.

The degeneration of the ganglion-cells is striking, and in most of them degeneration is quite advanced. The pronounced increase of the lipoid pigment is the most prominent feature of this degeneration; in fact, in some of the degenerated cells the cytoplasm is entirely filled with fat. By Bielschowsky's method it is seen that the neurofibrils are no longer continuous through the cell body, but in many cells are broken up into fine particles. Changes in a few bundles of nerve-fibres in the lenticulate nucleus and optic thalamus occur.

Hyperplasia of the glia is prominent, especially is the small variety with darkly stained nuclei in evidence, and areas are frequently encountered where these cells are grouped together in large numbers. A perivascular gliosis is visible in many instances. A considerable thickening of the walls of many of the vessels is discernible. Amyloid bodies are unusually plentiful, and groups of ten to twenty are frequently seen.

Cerebellum: Alterations could be detected in a few only of the Purkinje cells. The glia-cells are increased, especially in the molecular layer, and the superficial basal membrane is thickened. No appreciable fibre decrease is perceptible with the Weigert-Pal or Bielschowsky methods.

Medulla oblongata: The cells of the motor nuclei show no obvious deviation from the normal. In some of them a granular degeneration of the neurofibrils is apparent.

Spinal cord: Most of the cells of the anterior horns appear smaller than normal, but otherwise show no distinct alteration in any region of the cord. In a few of them an increase of the lipoid pigment is perceptible. A number of the cells of the posterior and lateral horns in the cervical region show a more extensive alteration. In the thoracic region a few of the cells of Clarke's column show chromatolysis, and some cells of the posterior horns pigmentary degeneration. In the upper lumbar cord, a small hæmorrhage is present in the vicinity of, but not extending into the central canal. Numerous amyloid bodies are visible in the posterior columns in all parts of the cord. A slight increase of glia is perceptible. A study of longitudinal sections show only a few typically degenerated fibres.

Peripheral nerves and spinal ganglia: A careful examination of the radialis, ulnaris, medianus, ischiadicus, cutaneous femoris posterior and spinal ganglia, failed to reveal any pathological alterations.

Case 2.—G. S., white, male, private U.S. Marine Corps. Was admitted August 11, 1900, and died December 6, 1912. His father suffered from alcoholic insanity and his mother was of a neurotic temperament. Patient was born in the State of Ohio in 1872. He began school at the age of 5 years and the childhood period of his life was uneventful. He enjoyed good physical health until the age of 20 years, when he had an attack of typhoid fever. The first choreiform movements were noticed at the age of 26. About July, 1900, he became hypochondriacal and gave evidence of persecutory ideas and irritability. Prior to that date no change in his disposition had been observed.

Upon admission to the hospital the patient appeared to be in fair physical health. Temperature and pulse were normal. Vision was good and the pupils reacted to light promptly and were equal and regular in outline. The skin and lymphatic glands were normal. The bones were large, but no anomalies or malformations were present. Examination of the internal organs failed to reveal any evidence of disease. The deep and superficial reflexes were exaggerated. No areas of tenderness; hearing and taste normal. Smell somewhat impaired. Urine: clear, acid; specific gravity 1025. No albumen, sugar or casts. Few leucocytes. Reaction time prolonged. Perceptions false. Memory poor. Reasoning and judgment impaired. Ideation is imperfect.

The emotional state was that of depression, hypochondriasis and a tendency at times towards hyperirritability. He was disposed occasionally to become violent in his attitude towards the patients and attendants.

When spoken to he failed to reply and walked away, or his replies were mumbling and incoherent. He was untidy with his clothing and personal appearance, and had difficulty in getting about. His head and hands were continually in motion, and owing to these irregular movements he generally required feeding. He usually manifested no interest in his surroundings, or gathered trash, with which he filled his pockets. He expectorated on his clothing, and when in bed picked at and destroyed the bed-clothing. The facial expression was constantly changing, frowning, winking, one side of the face was contracted, then the opposite angle of the mouth. The fingers, hands, arms, shoulders, knees, legs and neck muscles jerked, and the body was thrown from side to side.

A gradual mental and physical deterioration occurred, and the patient died December 6, 1912.

POST-MORTEM RECORD.

External examination.—Body was medium sized and well developed.

Internal examination.—Calvarium symmetrical, wall thickened in frontal and occipital regions, diploe compact. No roughening of inner surface. The dura mater was slightly thickened, smooth and not adherent to the skull cap or pia. The vessels of the pia were not prominent. The pia stripped readily, no opacity was present, and it appeared normal.

Brain: Weight 1,100 grm. Slight atrophy, but firm and of even consistency. The basal vessels are clear. The ventricles are not dilated, and ependymitis is absent.

Spinal cord: Appeared unusually small in size.

Thorax: Pericardium normal. Heart, weight 1,100 grm. Right auricle enlarged, wall thin. Tricuspid valve normal. Right ventricle normal. Pulmonary valve and artery normal. Left auricle somewhat enlarged. Mitral valve normal. Left ventricular wall thickened. Aortic leaflets slightly thickened. Lungs, pleural adhesions present. Emphysema, œdema and congestion in evidence.

Abdomen: Liver, weight 1,230 grm. Surface smooth, capsule normal. Passive congestion. Gall-bladder normal. Spleen, weight 150 grm. Capsule thickened, surface smooth, pulp soft and red in colour. Pancreas, stomach and intestines normal.

Genito-urinary tract: Kidneys, weight, right 150 grm., left 170 grm. Right kidney surface smooth, capsule strips readily, cortex thickened. Left kidney same condition. Bladder, mucous membrane somewhat congested.

MICROSCOPICAL EXAMINATION.

Precentral region: The pia is somewhat thickened and shows a hyperplasia of the connective tissue. No marked increase of cellular elements is visible.

Various alterations in the size, shape and staining reaction of many ganglion-cells throughout the cortex in this region is apparent. The Betz cells, however, for the most part appear quite normal. Some of these cells are swollen, their sides are rounded, giving them a circular aspect, others are small and shrivelled, the cytoplasm is broken and interrupted, and the nuclei are ill-defined. Many of the cells presented a faintness of staining, and in addition to this a homogeneous aspect, so that the cells present a uniform colour.

Chromatolytic changes are observed, and instead of the row-like appearance usually presented by the tigroid material, a fine dust is seen scattered irregularly throughout the cell, or the Nissl substance appears in long threads or is clumped. A deficiency or absence of chromophilic substance generally accompanies these changes. A considerable increase of pigment occurs in most of the cases. Changes are evident in the nuclei which show abnormalities in shape and appearance. Frequently eccentricity occurs. In some instances the nuclei are greatly enlarged, and in others but slight distension has occurred. The nucleoli are occasionally unusually large and stain metachromatically. Numerous cells show a twisting of the apical processes of the cells, giving them a corkscrew-shaped aspect. The dendritic processes are atrophic and apparently broken off. Many of the cells show evidence of vacuolation, numerous vacuoles at times occurring in a cell.

Disintegration of the neurofibrils is visible in degenerate cells. The tangential and interradiary fibres are reduced.

The neuroglia cells are greatly increased, mostly in the lower layers of the cortex. Many of the glia-cells present gross pathological changes. The protoplasm appears coarsely granular. The nucleus is shrunken and excessively stained; the chromatin substance is markedly increased; the granules enlarged, collected around the periphery of the nuclear membrane, or massed together, practically occupying the entire nucleus, in which instance the nucleus appears as an homogeneous, intensely stained blue mass. An accumulation of yellow pigment is frequently present in the protoplasm. Glia-cells are also encountered, having an angular, or rod-like nuclei. The nuclei present a triangular, or shrunken, rod-like appearance, and the protoplasm of these cells is disposed as long delicate processes; other glia-cells are met with having greatly enlarged nuclei. The nuclear membrane is considerably thinned and the caryoplasm achromatic, a delicate net-like structure is seen uniting the chromatin particles, and one or two metachromatically staining nucleoli are in evidence. The cytoplasm of these cells is quite perceptible, staining a violet shade, and numerous delicate processes extend from the cell body. Lipoid granules are usually observed lying within the cell body.

Glia-cells having a typical rod-like form are frequently encountered lying in close proximity to, or apparently within the cytoplasm of the cell body, or processes of degenerated ganglion-cells.

With Alzheimer's methods for the staining of glia-cells, the cytoplasm of the hypertrophic glia-cells is intensely and extraordinarily stained. Some of their processes are seen to be in direct relation to the blood-vessels, especially the capillaries.

Aside from this a number of processes extend in various directions from the cell body, some of which are short and broad, while others are thin, long, and pursue a rather tortuous course.

Weigert's stain for glia shows a hyperplasia of the glia fibres and the presence of fibrinoid granules.

Many of the vessels are twisted and tortuous. This twisting of the vessels causes them to appear constricted in some parts of their course.

The intima of the capillaries is more darkly stained than normal.

The adventitial spaces contain considerable disintegration products. A thickening of the adventitial connective tissue is evident, and the protoplasm of the adventitial cells contains lipoid substance.

In the first and second frontal gyri a slight hyperplasia of the pia is evident.

The alterations in the cells in this region are chiefly shrinkage of the cell, which predominated in the neurones of the lower layers. The contour of the cell is shrunken and distorted, and retro-action of the borders of the cell body between the processes not infrequently occurs, causing the cell body to assume an elongated, rod-like aspect. A well-defined net-like structure is discernible in the cell body, and is usually visible in the processes. The nucleus is darkly and homogeneously stained, often reduced in size and distorted. The nucleolus is pale and frequently oval in shape. Many of the large ganglion-cells are not shrunken, but show a marked change in the distribution of the Nissl substance throughout the cell. The chromophilic substance is observed at the base and sides of the cell body, or forming a rim around the periphery of the pyramid. In some instances the rim is continuous, and in others it consists of a number of separate masses. In most of these neurones the basal processes are more altered than the apical processes. The nucleus is ill-defined and the nuclear membrane cannot be demonstrated. The neurofibrils are considerably altered in some cells and indistinct in others. Disintegration of the tangential fibres is present. Proliferation of the neuroglia cells occurs, especially in the deeper layers of the cortex. The pathological changes in the glia-cells resemble those found in the precentral region. Many of the vessels show a hyperplasia of the adventitial cells and a fatty degeneration of the endothelial elements.

The cellular alterations in the cortex of the temporal and occipital regions are similar to those seen in the frontal convolutions, although less extensive. The alterations affect principally the deeper layers, but abnormalities can be detected throughout the depth of the cortex. Reduction in the tangential fibres is equally intense. However, the most marked changes in the cerebral cortex are in the frontal gyri and precentral convolution.

In the hippocampal region sclerotic changes are visible in most of the ganglion-cells. The cell bodies are deeply stained and the nuclei deformed and angular. Some cells are swollen and their nuclei enlarged. Granular disintegration of the neurofibrils occurs in some cells. Proliferation of the glia-cells is present, and slight thickening of the walls of many vessels.

The pathological changes in the optic thalamus are severe; somewhat less so in the caudate nucleus. The lenticulate nucleus is the most affected. The degeneration in the neurones is severe and extensive. A general chromatolysis is visible, and the majority of the cells shows an abnormal increase of lipoid substance. In others, sclerosis or shrinkage occurs, and numerous darkly stained coarse granules are perceptible in the cytoplasm and processes. The chromatin granules of the nuclei are increased in number, and vacuolar degeneration can be observed in some instances. The neurofibrils in many cells are seen to be discontinuous and appear as fine granules by the Bielschowsky method. The pronounced increase of the small non-fibre building glia-cells is striking. Large numbers of these cells are seen around and sometimes lying within the cytoplasm of ganglion-cells. A marked gliosis is seen in the vicinity of capillaries, the walls of which are thickened. The adventitial spaces of many of the vessels contain pigments; clusters of amyloid bodies are numerous.

Cerebellum: Some of the Purkinje cells show chromatolytic changes, and neurofibrillar disintegration is also apparent and in many cells.

Spinal cord: In the anterior horns only a few of the cells show slight alteration, but degenerative changes are more marked in the cells of the posterior horns throughout the cord. A number of amyloid bodies are present in the posterior columns. Only a few degenerated fibres are in evidence. No pathological changes can be detected in the spinal ganglia or peripheral nerves.

The anatomical findings in both cases were similar. Slight atrophy of the brain with increase of the spinal fluid, somewhat more marked, however, in the first case. Other than a moderate degree of thickening, the meninges appeared normal. Neither dilation of the paracœles or ependymitis of the lateral or fourth ventricle was present. The smallness in the size of the brain and spinal cord was a conspicuous feature in both cases.

Microscopically diffuse degenerative changes in the nerve-elements of the brain was evident. This degeneration was most severe in the optic thalamus, corpus striatum, the frontal and the pre- and post-central regions.

In reference to the medullated fibres of the cortex, a deficiency of the tangential fibres was especially noticeable, and the oblique fibres, forming the interradiary and supraradiary plexuses were similiarly affected. The radial fibres composing the radiations of Meynert were well preserved.

The ganglion-cells showed different types of degeneration. While acute degeneration occurred in many of the cells, sclerotic changes were apparently more frequent. The great increase of lipoid pigment within the cells was a prominent feature of the microscopic picture.

The Betz cells, with the exception of a few, were remarkably well-preserved throughout.

The changes in the neuroglia tissue were an enormous increase of the glia-cells and glia-fibres, especially in the lower layers of the cortex, the corpora striata and thalami, the cells having small pycnotic darkly staining nuclei being the predominating type.

The most obvious pathological alterations in the vessels were found in the lenticulate nuclei and thalami. The walls of many of the capillaries were greatly thickened and their lumen sometimes nearly obliterated. An extraordinary number of amyloid bodies were present in the posterior columns of the spinal cord, the thalami and lenticulate nuclei, but were more numerous in the first case.

In reviewing the literature, it is obvious that the only agreement which exists among investigators is that an organic change in the brain occurs. It has been the opinion of some that a diffuse or circumscribed encephalitis, or meningo-encephalitis, constitutes the pathological basis of the disease (Greppin, Oppenheim, Weidenhammer), while others attributed it to vascular alterations (Wollenberg). It seems probable that the meningeal and encephalitic conditions found at autopsy represented terminal complications in the disease rather than the cause of the symptoms.

Most of the writers on this subject have reported the occurrence of an atrophic process in the central nervous system, especially of the cortex of the cerebrum. Some writers (Stier, Kattwinkel) found the motor region most affected; Oppenheim and Hoppe, the central convolution, the parietal and occipital lobes. Other cases showed no atrophy microscopically. The results of most investigators coincide as to the occurrence of severe cellular degeneration in the cortex. This degeneration has been described in some cases as uniform throughout the cortex, while in other instances it was more intense in certain layers. Menzies found a degeneration of the cells in all the layers, but especially the deeper ones. Besta describes an alteration of the cells in the upper layers, although he considered this as secondary to a leptomeningitis. In the cases examined by Daddi, degeneration of the ganglion-cells occurred especially in the frontal and motor regions. Clarke found the pyramidal cells especially in the superficial layers of the central and frontal areas affected. Stier discovered a chronic degeneration of the small and medium-sized ganglion-cells of the second and third layers, and in Rusk's case, the medium-sized pyramidal cells showed the greatest variation from the normal. Kölpin found the cells of the outer granular layer, and the small pyramidal cells of the third layer degenerated to a greater extent than in the other layers. Modena observed that the large pyramidal cells of the cortex were slightly affected only, but pronounced chromatolysis and eccentricity of the nucleus prevailed in most of the small ones. Facklam, however, asserts that the small and large pyramidal cells were normal in a case examined by him. Many authors failed to detect any, or only a slight, pathological modification of the Betz cells (Stier, Greppin, Raecke, Kölpin, Rusk).

A number of writers have regarded hyperplasia of the glia as the characteristic alteration.

Collins found the glia increased, especially in the deeper layer, around the pyramidal cells and vessels. Clarke reports an increase in the amount of interstitial tissue and the number of neuroglia cells in the second and third layers; Menzies a slight coarseness of neuroglia in the first layer; Weidenhammer a hyperplasia of glia chiefly in the deeper layers; Schulz in the glia-cells, especially in the layer of large pyramids. Berkley found an increase of neuroglia in the medulla and spinal cord. Stier describes an increase of glia, and believes that, owing to an inherited anomaly of the motor cortex, the glia begin to proliferate in this region, especially in the layer of small and medium-sized ganglion-cells. He considers this proliferation as a primary process and the atrophy as secondary. Some writers, however, observed no increase of cellular elements in the cortex (Facklam). Kölpin found the marginal neuroglia somewhat thickened, but no marked increase of the glia elements was demonstrable.

Lannois and Paviot, Modena, and other investigators, especially in recent years, have observed, in addition to cortical degenerative changes, more or less severe alteration in the basal ganglia.

Margulies describes a hyperplasia of the glia and degeneration of the cells of the cortex and basal ganglia with atrophy of the tangential and supraradiary fibres. He is of the opinion that the muscular spasm is caused by irritation, which the proliferating glia exercise upon the nerve elements. From our present knowledge, however, of the rôle played by the glia in pathological processes, this hypothesis seems improbable.

In three cases examined by Alzheimer he found the most severe changes in the corpus striatum. Also in the subthalamic region the cells were greatly degenerated, somewhat less in the thalamus, pons, medulla, and spinal cord.

Morphological deviation in the architectonic of the cortex has been advanced as a possible etiological factor. However, if this were the case, it seems probable that evidence of the disease would be manifest from birth, whereas the symptoms do not occur until late in life and always assume a progressive character.

In conclusion, it may be stated that the pathology of chronic degenerative chorea consists not only in a degenerative process in the nervous elements of the cortex, but of the thalamus and corpus striatum.

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EXPLANATION OF PLATE.

FIG. 1.—Degenerated ganglion-cell from the precental gyrus. Toluidin blue. Zeiss Imm. $\frac{1}{12}$ oc. 3. The cell-bodies of the surrounding glia elements are filled with yellow pigment, and one of them is seen lying within the cytoplasm of the nerve cell.

FIG. 2.—Distorted pyramidal cell with eccentric nucleus, from the frontal region. Toluidin blue. Zeiss Imm. $\frac{1}{12}$ oc.

FIG. 3.—Nerve cell of the third cortical layer, frontal region. Toluidin blue. Zeiss Imm. $\frac{1}{12}$ oc. Much shrinking has occurred.

FIG. 4.—Contiguous degenerated ganglion-cells in paracentral region. Many glia-cells are seen in the vicinity of their base. Toluidin blue. Zeiss Imm. $\frac{1}{12}$ oc. 3.

FIG. 5.—Pyramidal cell from the anterior central convolution showing fine granular degeneration. Toluidin blue. Zeiss Imm. $\frac{1}{12}$ oc.

FIG. 6.—Ganglion-cell from paracentral region showing vacuolar degeneration. Toluidin blue. Zeiss Imm. $\frac{1}{12}$ oc.

FIG. 7.—Nerve cell from lenticulate nucleus showing extreme fatty degeneration.

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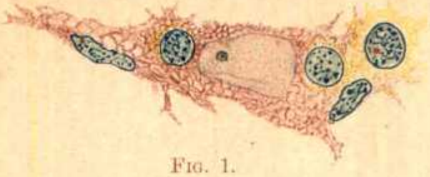

FIG. 1.

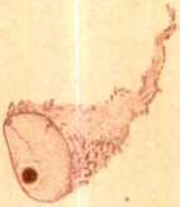

FIG. 2.

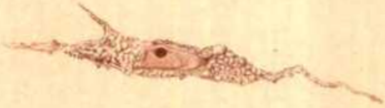

FIG. 3.

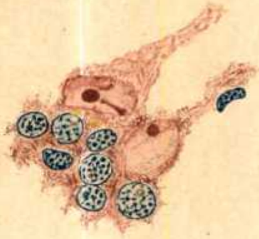

FIG. 4.

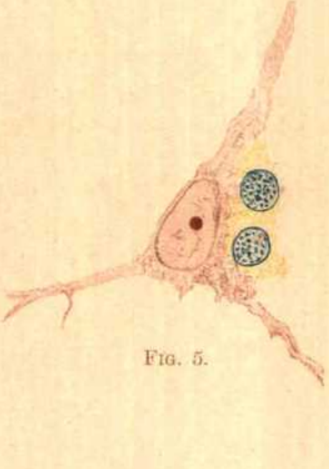

FIG. 5.

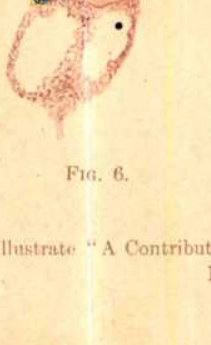

FIG. 6.

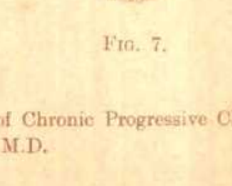

FIG. 7.

To illustrate "A Contribution to the Pathology of Chronic Progressive Chorea."
By J. A. F. PFEIFFER, M.D.

Bale & Danielsson, Ltd lith.

A CASE OF LANDRY'S PARALYSIS WITH ESPECIAL REFERENCE TO THE ANATOMICAL CHANGES.

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MORE than half a century has passed since the description by Landry, in 1859, of an increasing progressive form of paralysis, affecting the muscles of the legs and rapidly extending in turn to the arms and trunk, and producing death by paralysis of the muscles of respiration. The reflexes are lost, but the muscles retain a normal reaction to faradism. Muscular and special senses are not involved, and the sphincters remain intact. Slight fever, numbness and tingling in the fingers may be present. In Landry's case, no lesions were found in the brain or spinal cord at autopsy. To this affliction the name Landry's paralysis has been ascribed.

Since then a copious literature has accumulated, and numerous cases have been reported, simulating clinically to a greater or less extent in semiological features Landry's description.

From an etiological point of view, it is generally supposed that the affliction has a toxic basis. Bacteria have been discovered in a number of instances (Eisenlohr, Remlinger, Marie and Marinesco), and some investigators have attempted to isolate a specific organism (Nazari, Buzzard).

The first anatomical examination of Landry gave a negative result, and he postulated that the condition was without an anatomical foundation. In the older literature a number of cases are on record which were subjected to *post-mortem* examination and in which no lesions were found.

The explanation for the negative pathological findings in the older cases is obvious when we consider the fact that these examinations were made before the introduction of selective and improved methods for the staining of nervous tissue, especially the peripheral nerves. In addition to this the histological examinations were in several instances quite incomplete; even in the later literature many cases are recorded in which an examination of the peripheral nerves was not made.

In such instances it is plain that no definite conclusions could be deducted in reference to the morbid pathology.

If we consider the abundance of cases which have been reported in recent years, in which a complete pathological examination has been undertaken with improved methods, it becomes apparent that morbid changes can scarcely be regarded as negative in this type of paralysis.

It has, therefore, been the desire of investigators to establish some relation between the clinical manifestations and the pathological changes, and to discover the etiological factors in the production of the clinical picture. The question then arose whether the symptoms were due to changes in the peripheral or central nervous system. But the difficulty which has presented itself is the lack of uniformity and the variation in the descriptions of the pathological alterations.

Changes have been described in the cells of the anterior and posterior horns of the spinal cord, especially the anterior horns, with myelin degeneration in the central nervous system as well as the peripheral nerves. Degenerative changes have been reported in the anterior and posterior roots. Probably the most frequently described morbid condition has been a hyperæmia of both the spinal cord and meninges, associated with capillary hæmorrhages or perivascular infiltration. An intense diffuse inflammation of the spinal cord and meninges has been observed, accompanied by marked vascular infiltration and areas of softening. Changes confined exclusively to the peripheral nerves have been reported, and hyaline degeneration of the walls of the blood-vessels.

The numerous instances in which enlargement of the spleen and pleurisy with recent or old adhesions has been observed, is interesting.

Great importance has been attached to the changes in the spinal cord and brain, and consensus of opinion has been that the anatomical alterations in this condition are to be found in the central nervous system.

A number of authors have called attention to the possibility that the affection is essentially polyneuritic in character, and not dependent upon changes in the central nervous system. Dydynski has placed great importance upon the damage to the peripheral nerves, but believes that the central nervous system may also to a greater or less extent be involved. He explained the cause of the ascending character of the paralysis by the theory that the most important nerves possess the greatest resistance against toxins and are in consequence the last to become affected. Rolly, in a report of seven cases of Landry's paralysis, concluded that it was an acute type of polyneuritis. In one of his cases the changes were confined to the fine muscular branches. He laid great stress upon the examination of the peripheral nerves in all cases of acute ascending paralysis.

V. Leyden and Goldscheider concluded from the manifold anatomical changes, that the affection could assume a bulbar, medullar or neuritic form. They believed that a combination of any two of these conditions could occur and might begin in the peripheral nerves and ascend to the spinal cord. Saltmann suggests a separation of the condition into several forms depending on polyneuritis, myelitis, or without anatomical changes. Such a division might indicate different stages of the same process, depending upon the duration of the disease and the virulence of the toxin. Other authors believe that a close relation exists between poliomyelitis and the Landry symptom-complex. Wickmann states that the most of the fatal cases of acute poliomyelitis in the final stages of the disease present the symptoms of an acute ascending or descending paralysis. Harbitz and Scheel declare that many cases of so-called Landry's paralysis, or ascending paralysis, are severe cases of acute poliomyelitis, with the usual extension outside of the spinal cord. Mosny and Moutier believe that the Landry's symptom-complex corresponds anatomically to an encephalomyeloneuritis, or toxic infection of the entire neurons.

According to other authors, Landry's paralysis is only a clinical "symptom-complex" which may occur in diseases affecting different parts of the nervous system, viz., poliomyelitis, lyssa, polyneuritis, &c.

In view of the diversity of opinions in reference to this affection, a report of the following case seems appropriate, since it presented some interesting features, and inasmuch as a pathological examination with the latest methods was possible.

HISTORY OF ILLNESS.

Case 395.—Male, aged 24. German, stove fitter, single.

Family history.—Mother dead. Father living and healthy. Patient had nine brothers and sisters; six died in infancy; those living are healthy. No history of nervous or tubercular disease in the family.

Personal history.—Patient learned to walk between the second and third year of age. Successful with his studies at school. From 1908 to 1910 he served as a soldier in the German Army. He was not a heavy smoker and did not use alcohol to excess.

Past illnesses.—During childhood he had diphtheria and whooping cough. No history of eye or glandular diseases. The adult life of the patient was free from illness.

Present illness.—On the morning of January 4, 1912, the patient on rising observed that he had difficulty in walking. He did not recall having noticed any weakness in his lower extremities the day before. He suffered no pain whatever, but his legs felt heavy, and walking was so uncertain that, contrary to his usual custom, he used the street car in going to work. During the day he felt languid and faint. He could not sleep at night and was more comfortable when lying upon his back. On the morning of January 5 his condition was about the same, and he went to his work, but was compelled to return home about noon on account of the increasing weakness in his legs, and a few hours later could not stand without support. His appetite was extremely poor. No fever was noticed. His physician ordered him to bed.

On January 6 the paralysis was more marked and the patient uncomfortable and restless.

January 7: His physician ordered him to be sent immediately to the hospital. The paralysis extended to the upper extremities, being more pronounced in the left arm than the right arm.

January 8: Paralysis of the arms was complete, but no pain was felt by the patient, only discomfort from lying on his back. He suffered somewhat from headache, and a coated tongue.

January 9: Patient was very weak, but no new symptoms developed.

On the morning of January 10, the patient experienced difficulty in swallowing and was extremely weak. The paralysis extended to the muscles of the shoulders and neck, and difficulty in speaking supervened. About 4 p.m. he complained of dyspnœa and breathing became laboured. At 6.30 death occurred from respiratory paralysis.

PHYSICAL EXAMINATION.

The following examination of the patient was made on his admission to the hospital, January 7, 1912. Patient a young man of pale complexion and appeared to be well nourished. Muscles well developed. No excess of fat. Œdema, exanthema or scars absent.

Head: Eyes, nose, and ears normal.

Mouth: Tongue coated, teeth in fair condition. Pharynx and tonsils swollen and congested.

Neck: Normal.

Thorax: Normal in breadth. Somewhat flat. Expansion normal.

Lungs: Vesicular breathing. No rhonchi or other abnormal signs.

Heart: Action regular. Sounds intensified. Pulse regular and full.

Abdomen: Not sensitive to pressure. Liver and spleen could not be palpated.

Spinal column: No deformity present; not sensitive to pressure.

Urine analysis: The urine was regularly examined, but nothing pathological could be detected.

Examination of the spinal fluid: Colour normal. Three cells per cubic millimetre.

Wassermann test: With both blood and cerebrospinal fluid negative.

NEUROLOGICAL EXAMINATION.

Sight: Pupils react normally to light. Acuteness of vision $\frac{6}{6}$. No strabismus. Conjunctival reflex normal.

Hearing: Auditory apparatus in good condition (Weber and Rinne tests).

Smell: Normal.

Taste: Normal.

Upper extremities: The patient could raise his right arm with great effort only, and his left not more than 45°. Muscles very weak—left more so than the right. Dynamometer 10. Flexors and extensors similarly affected. Muscular atrophy absent.

Reflexes: Triceps—left less than right. Biceps—left less than right. Abdominal and cremasteric reflexes normal.

No pain upon pressure or other sensory disturbances could be elicited. Ataxia absent.

Lower extremities: Active movement impossible. No muscular atrophy.

Reflexes: Patellar and achilles lost. No sensory disturbances. Rectal and vesical sphincters intact.

AUTOPSY.

Body medium sized, well nourished and muscular. No œdema or scars were found.

Thorax: Upon opening the thorax the lungs sunk but slightly backward, and were adherent to the anterior wall of the thorax. The pleura was greatly thickened.

Lungs: Weight 1,190 grm. The upper lobe of left lung was soft in consistency. The lower lobe somewhat firm. Upon section the upper lobe was found to be emphysematous and considerably congested. The surface of the section was of dark grey colour. Upon pressure a thick grey secretion could be expelled from the bronchi and parenchyma. The mucous membrane of the bronchi was swollen and slightly congested. The upper and middle lobes of the right lung were soft in consistency, also the lower lobe in its peripheral portions. Upon section the upper and middle lobes were found to contain air.

In the firm portion of the inferior lobe several small pneumonic areas of consolidation were present.

Pericardium: A few drops of clear yellow fluid were present in the pericardial sac.

Heart: The heart was about the size of the fist of the corpse. Anteriorly the pericardial fat was greatly increased. The wall of the right ventricle was 0·7 cm. thick. The mitral cusps were thin and smooth. The endocardium was soft and glossy. Upon the epicardium of the left ventricle groups of blood clots were present. The wall of the left ventricle was 1½ cm. thick. The endocardium of the left ventricle was rough. The mitral valve was somewhat thickened, also the aortic leaflets. The intima at the beginning of the aorta was smooth. The aorta was quite elastic. Upon section of the heart, muscle was a dark reddish-brown colour.

Mouth, œsophagus, &c.: The mucous membrane of the floor of the mouth and cheeks was injected and the tonsils much enlarged. The crypts of the tonsils contained yellow soft masses. The glands at the roots of the tongue were hyperplastic. Upon section the tonsil was of a reddish-grey colour. A small area about the size of a pea and of a greenish-grey colour was found in the right tonsil. The mucous membrane of the œsophagus was pale and smooth. The thyroid gland appeared normal.

Abdomen: Upon opening the abdomen, fibrous adhesions were found between the diaphragm, liver, and peritoneum.

Stomach: The mucous membrane was greyish-red in colour and contained petechial hæmorrhages.

Intestines: The mucous membrane of the duodenum somewhat thickened at the pyloric end. Here and there in the small intestines isolated areas of irregular mucous membrane were found. Otherwise normal in appearance. The lymph follicles were not enlarged. Peyer's patches appear normal. A thick secretion covered the lower portion of the large intestines. The mesenteric glands were somewhat enlarged.

Liver: Weight, 2,200 grm. The liver was firmly adherent to the diaphragm on the right side. Upon section it was found that small yellowish spots were scattered throughout the organ. Considerable congestion was present. The gall-bladder contained several dark orange coloured gall-stones.

Spleen: Weight, 500 grm. Enlarged. Adherent to the neighbouring organs by thick bands. The capsule was thickened, consistency soft. Upon section the pulp was dark red in colour and congested, and the cut surface covered with a thick dark reddish-grey fluid. The follicles were quite evident.

Pancreas: Soft in consistency and of greyish colour. Between the spinal column and the pancreas many enlarged lymph glands of a yellowish-grey colour were present.

Suprarenal glands: Normal in appearance.

Kidneys: Weight, 320 grm. Firm in consistency. Capsule strips readily. The surface was reddish in colour. Upon section the parenchyma appeared of a bluish-red colour. The cortices were thickened. The pelves and calices congested and filled with a thick greyish-yellow secretion.

Bladder: Normal.

The muscles of the thorax and abdomen were unusually dry.

Head.—Calvarium: Symmetrical. Wall, 6 mm. in thickness. Diploe porous.

Dura mater: Tense, smooth, and unusually moist throughout.

Pia mater: Somewhat thickened in the frontal region of the left hemisphere, glossy and tender over the entire surface of the brain.

Brain: Macroscopically nothing pathological could be found.

Spinal cord: Upon opening the spinal canal some fresh coagulated blood was found in the lower portion. Otherwise the spinal cord appeared normal.

BACTERIOLOGIAL EXAMINATION.

Cultures were made from the spleen and a streptococcus isolated.

ANATOMICAL DIAGNOSIS.

Consolidated areas in inferior lobe of left lung, Abscess of the pharyngeal tonsils. Pleuritic and peritoneal adhesions. Spleen greatly enlarged (septic splenic tumour). Congestion of kidneys.

MICROSCOPICAL STUDY.

Various parts of the central nervous system and the peripheral nerves were fixed in different fluids; namely, formol, alcohol, Weigert's mordant and Orth's fluid.

The parts of the nerves were labelled by spreading them out upon strips of cardboard, to which they tenaciously clung.

The following staining methods were used: Nissl toluidin blue; polychrome methylene blue; Mallory's hæmatoxylin; Marchi; Bielschowsky; Sudan III; Van Gieson's hæmatoxylin-eosin; Weigert's myelin-sheath, &c.

Meninges: No infiltration or pathological changes could be found.

Brain: Sections from different parts of the brain were studied by the Nissl toluidin blue, Bielschowsky and other methods of staining, and the changes which occurred in the cells, the neuroglia, and the vessels will be considered.

An examination of sections from the paracentral lobe reveals the fact that the giant cells of Betz are well preserved and contain well-defined tigroid masses in more or less row-like arrangement in the cell body and dendrites.

A variable amount of change in some of the pyramidal cells, other than the Betz cells, is present, largely confined, however, to the pyramidal cells of the ganglionic and multiform layers of the cortex. The tigroid bodies have undergone disintegration. In some instances a general chromatolysis has occurred, but in many cases the bodies in the interior part of the cells are affected more than those peripherally placed, i.e., a central chromatolysis is present. In the cells in which a general chromatolysis has occurred, a row of small irregularly defined and disintegrated bodies can usually be seen around the periphery of the cell, while here and there cells in which the chromophilic bodies have vanished, can be found. Lying among the disintegrated tigroid bodies, granules of various sizes and shape can be seen. Sometimes large irregular masses occur, and often small bodies grouped together are encountered. In some instances the disintegration is of such a character that extremely fine granulations are present. The nuclei also present deviations from the normal appearance. The nucleus is in some instances swollen, and the nucleoli are not stained. Shrunken nuclei and nuclei with an eccentric position or displacement to the periphery of the cell are seen.

A study of the cell pigment (lipoid material) which forms an important element of the ganglion-cells, shows no increase in this substance. The quantity of this pigment normally varies considerably in different cells. The large pyramidal cells of the cortex and the cells of the anterior horn of the spinal cord normally show a regular amount of this substance, while others, as the granular cells and small pyramids, contain very little pigment. This pigment increases with age. In youth it is small in amount, while in old age it frequently fills a great part of the cell body. Care is necessary in the study of this lipoid substance when stained only by the Nissl method, as it usually appears as an almost clear and minutely subdivided area in the body of the cell, and at first sight might lead one to think that an extreme form of vacuolization of the nerve-cell had occurred. Also in those instances in which the tigroid bodies are intensely stained, equal amount of the substance may appear quite different, according as the tigroid present is abundant or scanty.

With the Bielschowsky method for the study of neurofibrils, no change in these elements can be detected in most of the cells.

A hyperplasia of neuroglia-cells can be observed in the neighbourhood of degenerated ganglion-cells, and here and there glia rasen are in evidence. No vascular changes present.

Cerebellum: No pathological changes can be detected.

Medulla oblongata: The cells of the motor nuclei and of the formatio reticularis retain a normal appearance. A few of the cells of the nucleus gracilis, and of the nucleus cuneatus, show changes similar to those occurring in the cells of the lower layers of the cortex —that is, swelling of the chromophilic bodies, granular disintegration, shrinking and displacement of the nuclei. No degenerative changes or falling out of fibres could be found.

Spinal cord: Numerous sections from the cervical, dorsal, and lumbar regions of the spinal cord were prepared by methods for the study of pathological changes in the cellular elements, and alterations in the axis cylinders and medullary sheaths.

In the cervical region of the spinal cord the motor cells of the anterior horn show no alteration. The tigroid corpuscles are well defined, and retain their more or less characteristic row-like disposition in the cell body and dendrites. The nuclei are centrally situated, and no pathological changes can be seen. No abnormal increase in pigment is present. Some of the cells of the lateral horns, however, are swollen and show chromatolytic changes; the typical row-like arrangements of the Nissl bodies is lost, and they have undergone granular disintegration. The tigrolysis seems to be of a central type in most of the cells which show changes. The nuclei of some cells stain diffusely blue by the Nissl method, while other nuclei are swollen and refuse to take the blue stain. Occasionally slight fragmentation can be observed. The nucleoli present no marked alteration. In the posterior horns a few cells are found which show changes similar to those which occurred in some of the cells of the lateral horns.

In the thoracic region the cells of the anterior horns are likewise remarkably well preserved. Here and there a cell is encountered in which a row-like disposition of the tigroid corpuscles is disturbed, but otherwise no alterations can be seen. Slight granular disintegration in a few of the cells of the nucleus dorsalis is evident.

The motor cells of the anterior horns in the lumbar region present a normal appearance. A few of the cells in the posterior horns show changes of a similar character to those which have been described as occurring in the lateral horns of the cervical cord.

A painstaking examination of numerous longitudinal and cross sections from the cervical, dorsal, and lumbar cord revealed no degenerated nerve fibres.

Spinal nerve roots: In Nissl preparations an increase in cells appeared to exist in many of the roots. By larger magnification it is seen that this increase of cellular elements is due to the presence of polyblasts and "gitter" cells.

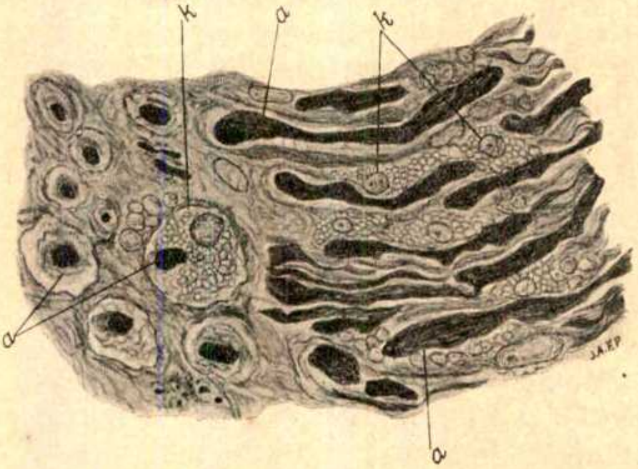

FIG. 1.—Bielschowsky method. Zeiss homo. Imm. $\frac{1}{16}$ oc. 1. From the crural nerve. Showing "körnchen" cells within the sheath of Schwann. *k*, "körnchen" cell; *a*, axis cylinder.

These changes are evident in the different roots and in the cauda equina, and are quite identical with those occurring in the peripheral nerves. The infiltration in the roots ceases somewhat before the point of their exit through the pia.

Peripheral nerves: For the study of the peripheral nerves the staining methods for the demonstration of the cellular elements, the medullary sheath and axis cylinder were applied. At the outset it could be readily noted that the changes in the brachial plexus and nervus cruralis were more marked than in the tibialis and peroneus. When sections were made with the microtome, numerous round and long areas of a greyish colour could be observed. By a low magnification it is evident that the changes in the nerves are quite irregular, some bundles being intensely infiltrated, while others remain apparently unaffected.

The polychrome methylene blue stain was applied for the study of the elements of the nerves, since they, especially of the perineurium and endoneurium, take an important part in pathological processes in the peripheral nerves. A study of the epineurium shows it to be much infiltrated with polyblasts and "körnchenzellen." In some areas the infiltration is more pronounced than in others, and lymphocytes, polyblasts, and "gitter" cells are crowded together so closely as to almost exclude other structures from view. Especially is this noticeable in the region of blood-vessels. Many "mast" cells are seen lying between the fat cells, in some instances collected together in masses. Large cells with horse-shoe shaped nuclei are occasionally encountered. Proliferation of the cellular elements is present.

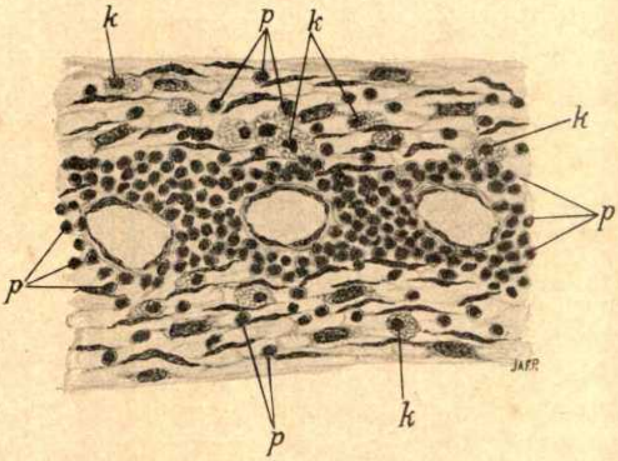

FIG. 2.—Polychrome methylene blue stain. Leitz obj. 6, oc. 1. From the peroneus nerve. Showing perivascular infiltration with "körnchen" cells and polyblasts. *k*, "körnchen" cell; *p*, polyblast.

The infiltration of the perineurium is even more pronounced. Here, as in the epineurium the polyblasts are prominent, and various stages of their development into "körnchenzellen" is in many areas beautifully illustrated. A proliferation of the cellular elements can be observed, their protoplasmic processes are more deeply stained and can be often traced for a considerable distance. "Körnchenzellen" are frequently seen in close proximity to these cells, to which they are applied. In the endoneurium, polyblasts and "körnchenzellen" are encountered in large numbers lying between lamellæ, and in the perineural lymph space. Proliferation of the endothelial and fixed connective tissue cells is quite evident. In cross section the protoplasmic processes of the profilerated fixed connective tissue cells can be seen surrounding several nerve fibres. The Schwann cells are only slightly proliferated. The similarity existing between the Schwann cells and fixed connective tissue cells often makes it difficult to distinguish the former from the latter; in fact, at times they cannot be differentiated.

With the Marchi method, an increase of the Elzholz bodies between the myelin-sheath and the sheath of Schwann can be seen. In Marchi preparations which have been counter-stained with safranine, these bodies are more evident, and the neurokeratin net, in reference to the existence of which much discussion has occurred in the past, is brought out prominently.

By Van Gieson's stain—besides the intensely red stained connective tissue—the cellular elements are also beautifully stained. The darkly stained nuclei of the polyblasts and "körnchenzellen" are especially pronounced, and the net-like protoplasm of the "körnchenzellen" is quite discernible.

By the Sudan III method, the "körnchenzellen" are seen to be filled with yellowish stained lipoid material.

An examination of numerous preparations by the Bielschowsky method show the axis cylinders to be uninterrupted in their course, and presenting a normal aspect. Whilst occasionally a slight fragmentary degeneration in a fibre, or here and there a newly-formed axis cylinder process, or considerable irregularity in the size of a fibre can be found; as similar changes have been frequently observed in normal nerve fibres, they cannot be considered as pathological. The polyblasts and "körnchenzellen" are remarkably well stained by this method, and the pronounced infiltration quite perceptible. Although the axis cylinders appear themselves intact, a careful examination reveals the interesting fact that the medullary sheath has become invaded by "gitter" cells, which in cross section of the fibres, can be seen lying within the sheath of Schwann.

CONCLUSIONS.

The changes in the peripheral nerves on microscopical examination, are most interesting, and emphasize the importance of an examination of the peripheral nerves in all cases of acute spreading paralysis, as it seems most probable that the pathology of this condition *per se* is to be looked for in the peripheral nervous system.

In this case the pathological findings are those of an interstitial neuritis, affecting the nerve roots and peripheral nerve stems.

It is also interesting to notice that in spite of the existence of this interstitial neuritis, no sensory symptoms or pain on pressure occurred.

The motor cells were well preserved through the central nervous system, and the cellular changes which were present could hardly be regarded as having any direct relation to the paralysis, as such cellular alterations are frequently found in other conditions not associated with acute spreading paralysis.

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DUCTLESS GLANDS AND THE NERVOUS SYSTEM.

The Pituitary Body and its Disorders. By HARVEY CUSHING, M.D. Philadelphia: J. P. Lippincott Co., 1912.

The Internal Secretory Organs. By Professor ARTUR BIEDL, of Vienna. English Translation by LINDA FORSTER, and Preface by LEONARD WILLIAMS, M.D. London: John Bale, Sons and Danielsson, 1912.

Innere Sekretion, ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie. Von Professor ARTUR BIEDL. Zweite neubearbeitete Auflage mit 131 Textfiguren und 20 mehrfarbigen Abbildungen auf 8 Tafeln. Berlin und Wien: Urban und Schwarzenberg, 1913.

DUCTLESS glands are in the present day theory of medicine as vaccines in its practice. There is little honest knowledge of either, yet all features of health and disease may be lightly ascribed to the one, and every ailment finds its golden hope of cure by injections of the other.

The books discussed in these pages will do much to dislodge confusion and ignorance, for they give a fair statement of what is known of the ductless glands, and they are written by men who rank among the chief authorities living on the subjects with which they deal. Cushing has modelled his treatise in the form adopted by Pierre Marie, Addison, and the great writers of the past, a separate account of each of a series of clinical cases being supplemented by the author's personal interpretation of the phenomena, so far as that can be based upon physiological experiment and pathological analysis. It is a clear record of fact, and while the evidence is marshalled to lead to definite conclusions, yet it is so displayed that criticism can at once disentangle the proved from the supposed and stop short, if it cares, of agreement with the final judgment. Original work has the advantage of this directness and simplicity, for it gives the outlook of a single mind.

Biedl attempts a more spacious task. Writing from the physiological point of view and not as Cushing, alert for every point that may tell in the diagnosis and treatment of clinical disease, he assembles all the observations that have ever been made on the ductless glands, in comparative anatomy, in chemistry, pathology, and especially in the laboratories of experimental physiology. The host of papers so called up is nearly 4,000 strong, and its catalogue alone occupies more than 100 pages, a quarter of the entire book. But each in the multitude speaks as loudly as his fellow, and it is hard to pick out the main theme amid the babel of voices. In his desire to be disinterested and fair, Biedl has gone almost too far and produced rather an index catalogue than what one would have desired, a reasoned exposition of the views of the Viennese school, whose workers, with Biedl at their head, have explored every part of this wide field of labour. Worst of all is the extreme deference in the body of the book to that tedious custom which in physiology couples every observation with some man's name, as though it were a personal opinion that is quoted rather than a scientific demonstration of a fact. The result is as baffling as the walls of a railway station are to the traveller who, seeking to know where he is, hunts in vain for the name of the town amid the patchwork of advertisements. Time must establish a saner practice in this respect and teach the wisdom of what was written by Sir Thomas Brown in preface to Pseudodoxia Epidemica, "For Knowledge is made by Oblivion, and to purchase a clear and warrantable body of Truth, we must forget and part with much we know."

The English translation is somewhat unlucky in the time of its publication. Appearing at the close of 1912, though made from the first edition of the German text in 1910, it barely antedates Biedl's second edition. The latter is a great improvement on the first, printed in much pleasanter form, enlarged to two volumes and nearly twice its original size, and freely illustrated with reproductions from the chief papers in pathology, comparative anatomy, and physiology, so that the reader loses much by being confined to the English of the first translation. But the translator, Linda Forster, has done the work well. Slight mistakes catch the eye here and there. "Darmanhangsdrüse" (p. 13) are not the glands of the appendix, and despite the statement of p. 16 iodothyrin does not occur in the adrenals. "Autonomic" was the word employed by Langley to designate Gaskell's visceral nerves, and the translator brings this back again from the German into English with the needless change to "autonomous." Acquaintance with physiology would have saved this slip, which, like several others, shows ignorance of English terminology rather than difficulty with the German text.

A brief abstract of the main teaching of these two books may be of interest to readers of BRAIN, for the pathology of the ductless glands touches neurology closely at many points.

THE PITUITARY GLAND.

Roughly, each decade has marked a great stride forward in the knowledge of this gland; 1889 brought the association of acromegaly with disease of the gland by Pierre Marie and Marinesco, the French clinician believing the main fault to be the loss of the secreting gland substance. In 1900 came the clinical recognition by Babinski and Fröhlich of the fatty eunuchoid condition, "dystrophia adiposogenitalis," that may be related to an undoubted atrophy or destruction of the gland. In 1910 Cushing gave the Harvey Lecture which has been expanded into this present book.

Physiological experiments have in the meantime established the fact that from the posterior "nervous" part of the pituitary gland can be extracted an active principle which stimulates all plain muscle to contraction [10], the arteries of the lung as well as those of the systemic vessels (Dale [3]), and which excites some gland cells to prompt secretion, notably those of the kidney and mammary gland; but these observations at present have little value in the discussion of the clinical problem and their meaning is altogether obscure.

For the adrenal gland a law has been clearly proved that stimulation, whether it be of gland-cell or of muscle, by the active principle, adrenalin, can occur only in tissues innervated by sympathetic nerves, and that the reaction caused in them is almost the same as that to the nervous impulse. No such rule relating the action of pituitary extract applies to any part of the nervous system. At present, therefore, no guess can be hazarded as to why this substance is produced in the gland and excreted into the body; indeed, its stimulating property may be quite accidental to the gland extract, and in no way concerned with the true function of the cells.

The pituitary is an extremely complex mass of tissue. In front is the real glandular mass, the pars anterior, most richly vascularized, and containing at least two different types of cell, the one staining blue with hæmatoxylin and eosin and the other a distinctive red. It is not known whether the red eosinophile cell is morphologically and physiologically distinct from the blue (chromophobe), or whether it simply derives its colour from a special phase of secretory activity. Behind lies the pars nervosa, tissue of an indeterminate character, like neuroglia but with very few nucleated cells. The anterior crescentic mass envelopes the pars nervosa, and between the two is a cleft lined on either side by a deep glandular layer, the pars intermedia, which differs from the pars anterior in that its cells are not packed compactly one against the other but resemble in their arrangement those of the thyroid gland, alveolar spaces being formed by distension with a colloid material.

The active principle, obtained by grinding with sand and boiling with saline solution, is yielded by the pars nervosa only. Eosinophile colloid material seems to be secreted in abundance from the true glandular cells, those of the pars anterior as well as those of the pars intermedia. Herring believes that the secretion passes, probably undergoing some change in the meantime, through the pars nervosa and thence by lymphatic clefts into the third cerebral ventricle and the system of the cerebrospinal fluid circulation [7]. This has not been fully proved to take place, whereas eosinophile colloid material can always be readily demonstrated in the rich capillary network of the glandular anterior part. Perhaps the colloid material is passed directly into the blood-stream; if such were the case the colloid would have nothing to do with the pars nervosa nor with the active principle obtained from the latter, of which alone the properties have been studied, and there would be no knowledge at all of the functions of the pars glandularis.

Cushing has recently endeavoured to show that the secretion from the pituitary is controlled by the cervical sympathetic nerve, but the experiments that he brings forward are of a very doubtful nature [2].

The clinical phenomena produced by disease of the gland are two-fold, those caused by direct pressure of its growth on neighbouring structures, such as the optic nerve, and those which are exhibited by the body generally as the result of too abundant or too scanty pituitary secretion. Symptoms of the second group, so far as is known, appear only in the slow changes of the form and growth of the body, whereby the normal type of manhood is perverted to the acromegalic giant or to a lethargic, eunuchoid creature overgrown with fat. This in itself is amazing enough, that a chemical secretion can slowly act with some mysterious power upon the texture of our bodies and alter its entire pattern.

But the pituitary has an abundant blood-supply, and its glandular cells pour out daily a considerable quantity of eosinophile material. Still greater must be the excretion of the thyroid from its larger bulk; while it has been proved by direct experiment that adrenalin is discharged into the blood from the medullary cells of the adrenal with almost every emotional and vasomotor reflex. Hence there may be other and speedier actions than those concerned in bodily growth. Other metabolic affairs are controlled by the secretions of the ductless glands; and from the pathological observations of the slow changes wrought by glandular disease arises a fresh conception of physiological activity, that growth, metabolism, muscular tone, indeed much of the steady regulation of the life that burns within and gives us being, results from the daily interplay of these glandular secretions which each and all in their part restrain or accelerate the activities of the various tissues, and so maintain the normal type. This aspect of the question will be referred to again later in considering the meaning of pluriglandular insufficiency.

Cushing regards acromegaly as the index of excessive secretion by the pituitary; diminished secretion has its special clinical features of obesity with eunuchoid changes, and may be caused by adenomata or tumours destroying the pituitary directly. The same result may be caused indirectly as the result of pressure by cerebral growths. Acromegaly is then comparable with exophthalmic goitre, and the second condition with myxœdema.

In these glandular diseases affixes are needed with the noun to denote the state of plus or minus secretory activity. General use accepts hyper- and hypo-, although they are found to be difficult to distinguish from one another in speech, and in the case of the pituitary lead to a slight confusion with the hypophysis itself. There is need of a pair of words that shall be in sharper contrast one with another, and it therefore seems better to take the prepositions *super* and *sub*, which give the desired contrast.

Acromegaly is assumed by Cushing to indicate superpituitarism. The classical case of subpituitarism is that reported by Madelung, a girl aged 9 who was shot in the eye by a rifle bullet which lodged in the sella turcica. She failed to grow, and became exceedingly obese. Very similar is the result in young animals, according to Cushing (though this is denied by Horsley [8]), when the pituitary is experimentally damaged. He gives the following list of changes caused by subpituitarism in children or young adults: infantilism of the sexual organs, absence of pubic and axillary hairs, adiposity, especially of the subcutaneous fat, a dry skin, polyuria, depressed temperature, but a febrile rise of two or three degrees upon intramuscular injection of an extract of the anterior lobe of the pituitary gland, increased tolerance of carbohydrates, so that 200 or 300 grm. of glucose by the mouth do not cause glycosuria. In the adult these phenomena may occur independently (Fröhlich's type), or develop as the last stage of exhaustion in a gland which had in its earlier spendthrift excess produced acromegaly. Good results are said to have been obtained by feeding with pituitary gland extract in these cases, though much larger doses are required than have generally been tried in England.[1]

Especially interesting is Cushing's account of adenomata of the pituitary. These benign growths are common in the adrenal, where they cause no symptoms; in the thyroid, where they may cause pressure on the trachea and become the seat of cystic or hæmorrhagic degeneration, and they are not rare in the pituitary. Their cells never excrete with such activity as to cause respectively the features of exophthalmic goitre or acromegaly. But in the pituitary they induce early pressure symptoms, bitemporal headache by distension of the dura mater enveloping the sella turcica, blindness or temporal hemianopia by pressure on the optic chiasma, and often subpituitarism by pressure on the rest of the healthy gland. Surgical treatment must be early, to preserve sight and save the gland. Cushing performs a sellar decompression, driving a tunnel from a submucous incision beneath the upper lip, up through the septum nasi and the sphenoidal sinuses, to expose the gland by reflecting its dura mater. This allows the adenoma to grow downwards, and as a rule suffices. Sight returns in a few days with the escape of the optic nerve from pressure.

Cushing describes in all forty-seven clinical cases of pituitary disease, of which twenty were proved by the microscope to be due to adenomatous growths causing subpituitarism. Of these forty-seven, 10 per cent. were Jews. The question is not raised, but it would be interesting to learn whether Jews as a race are particularly liable to pituitary derangements.

THE ADRENAL GLANDS.

It was in respect of these organs that the riddle of the ductless glands was first proposed by Addison's clinical observations in the disease that has since borne his name; and physiological work of the last twenty years, aided by the arguments of developmental anatomy, has won far clearer knowledge of the adrenals than it has of the other ductless glands. In this instance physiology has outstripped clinical pathology, while the latter has been unable as yet to make use of the discoveries of the physiologist. But it is well to remember that even in this later work, as in all the advances of knowledge of the ductless glands, the first promptings came from clinical observations. George Oliver thought that he had observed constriction of the vessels at the wrist in man when suprarenal gland extract was taken by the mouth. Perhaps the observation was erroneous, but it inspired him to seek Schäfer's aid in testing its truth by direct records of the blood pressure in animals, and the result of their joint work opened up new country, which has since been intimately explored by the many investigators who followed in their footsteps.

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[1] Cushing employs a dry powdered extract obtained after passage of the entire fresh bovine gland through a Buchner press. Of this 30 grains may be given daily, that is the equivalent each day of about 150 entire fresh pituitary glands. This corresponds roughly to 1,500 daily of Burroughs and Wellcome's tabloids, of which 10 contain the extractives of one entire gland. Cases of subpituitarism are very tolerant of sugar, from which Cushing deduces a test for the adequacy of the treatment, namely, that pituitary extract shall be pushed until sugar appears in the urine on a meal of 150 grm. of dextrose. This in one case required a daily consumption of 500 entire glands.

Balfour recognized the chief landmark when he saw that the cells of the adrenal medulla are derived from the same source as those of the sympathetic ganglia. This, indeed, is the peculiar interest of the gland, that it is practically a part of the nervous system.

The nature of this relationship has been worked out chiefly by the Cambridge School of Physiology, where the brilliant paper by Gaskell [5] in 1886 lit an eager interest in the visceral nerves that year by year has given forth more light. Gaskell challenged the old teaching, founded on Bichat's academic generalizations, which regarded the vegetative or sympathetic nervous system as a self-sufficing machinery for regulating the affairs of the viscera and almost independent of the central nervous system. Nowadays it is difficult to realise how deeply rooted was this opinion thirty years ago, and how widely it influenced all thought of the time as an almost axiomatic truth. Gaskell restored the monarchy of the central nervous system, showing that all the knotted complexity of the visceral nerves could be unravelled into single constituent strands arising from the spinal cord and carrying the dominant impulses of its central control. His, too, was the first broad classification of the nerves efferent from the brain and spinal cord. He showed that, while the motor nerves to the striped muscles connected with the skeleton issue in all the anterior roots, those to the unstriped muscle of the blood-vessels and viscera and to gland-cells do not flow out in a continuous series of anterior roots down the length of the spinal cord, but appear in three divisions, which are separated one from the other by the nerve-roots of the fore and hind limb plexuses. These visceral nerves all bear ganglion-cell relays on their course from spinal cord to peripheral tissue; by that they are distinguished from the skeletal nerves, and to that is due the anatomical complexity of their distribution. Langley accomplished the difficult task of analysing all the finer details of these nervous tracts, and he has introduced a fresh

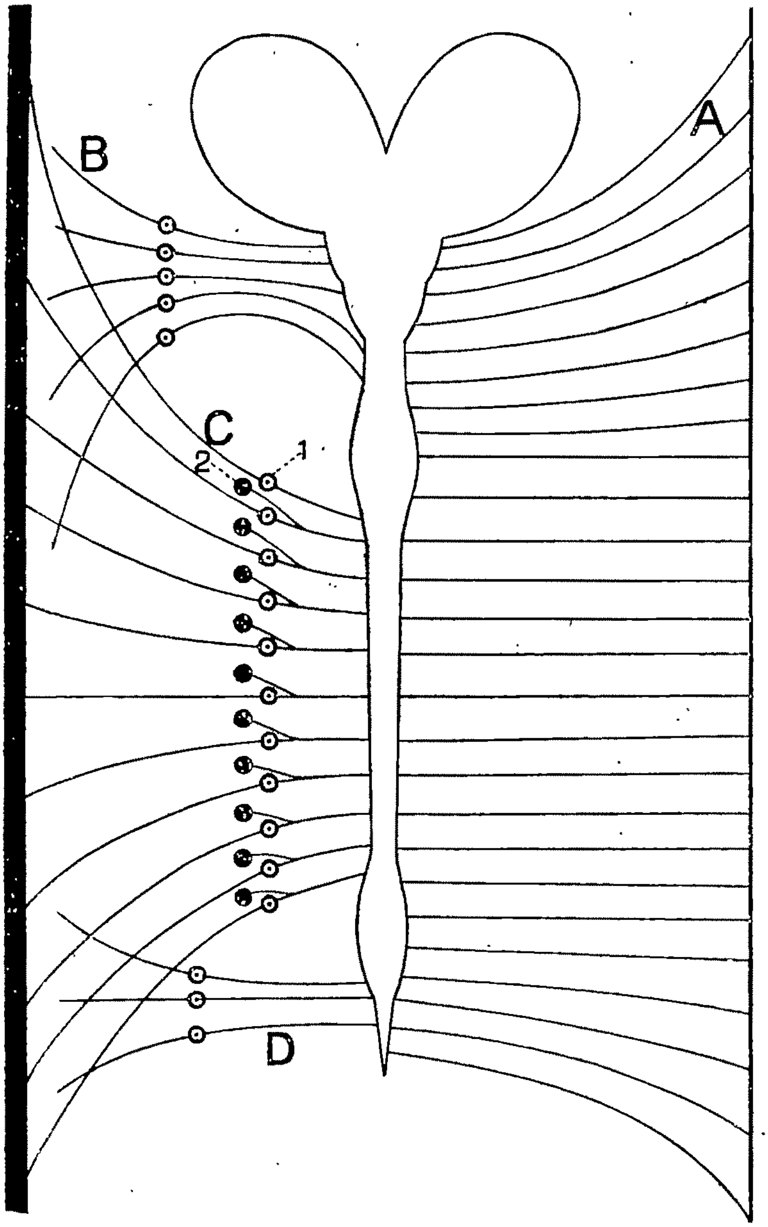

Diagram of the Nerves Efferent from the Central Nervous System in the Mammal.

A, the non-ganglionated ordinary motor nerves to striped muscle, which are distributed segmentally. On the left side these are omitted for simplicity, and only the autonomic or ganglionated visceral nerves to plain muscle are indicated.

Of these, B is the cranio-cervical outflow in the vagus, &c.; C, the thoracico-lumbar or sympathetic proper; D, the sacral outflow, or pelvic visceral nerve to the bladder and colon. All these subdivisions contain both motor and inhibitory nerves.

C_1 is the sympathetic ganglion-cell; C_2 the paraganglion-cell secreting adrenalin, the chief mass of these being concentrated to form the medulla of the adrenal gland, though a few, even in adult life, may be found elsewhere in relation to the various sympathetic ganglia. The black rectangle innervated by the nerves from the cells C_1 represents the mass of plain muscle which is also stimulated by adrenalin, that is by the secretion of C_2.

Afferent sensory nerves and their posterior root ganglia are all omitted from the diagram. Their course from the viscera is not clearly known.

nomenclature, according to which the entire group of ganglionated visceral nerves is styled the autonomic system; in this are the three subdivisions of the cranio-cervical, the thoracico-lumbar, and the sacral root outflows (see diagram). To the thoracico-lumbar outflow is restricted the old term of the sympathetic.

Now the entire mass of plain muscle united with thoracico-lumbar or sympathetic nerves shows a remarkable reaction to the active principle extracted from the medullary cells of the adrenal. It, and it alone reacts to adrenalin; and the reaction is identical with that to electrical stimulation of the sympathetic nerves. This holds true both for contraction and for relaxation, and for muscles so far asunder in physiological differentiation as those of the rhythmically pulsatile heart or of the tenaciously closed sphincter urethræ. Further, the medullary cells have been shown to discharge adrenalin into the blood-stream, and to do so as the direct result of excitation of the splanchnic nerves which supply the glands. This they are continually doing in the various vascular reflexes.

It is therefore clear that there are two closely related types of cells connected with the primary preganglionic sympathetic fibres coming from the spinal cord:—

(1) The sympathetic ganglion cell, which is distally united with the plain muscle by its axon process, and so provides a path for the nervous impulse.

(2) The medullary or paraganglion-cell, which is not in connection with the muscle but is equally innervated from the spinal cord, and secretes a chemical substance into the blood that can produce an identical excitation of the muscle through its myoneural junction.

These cells (1) and (2), are as brother and sister to one another, being in the closest kinship of morphological parentage. Life can be maintained though all the ganglion-cells (1) are removed; death results from cardio-vascular failure when the adrenal glands, that is the cells of the cortex and cells (2) have been excised. In the moribund animal, after removal of the adrenal glands, stimulation of the vaso-constrictor nerves is almost without effect, because the muscles of the blood-vessels have lost their tone. It may be that the cells (1) and (2) were once identical, and that the liberation of adrenalin was an essential part of the nervous impulse; but now the two processes are carried out separately by separate anatomical units. The paraganglion-cell (2) excretes the adrenalin that maintains the muscle at a fair level of tone for its routine activities; the nervous impulse (1) effects the rapid alterations from this level that may be required suddenly in special actions of the animal. Roughly, one may compare the muscle to the string of a violin that must be tightened up to its appropriate pitch before the fingers can evoke the rapidly changing notes.

Beyond such rough analysis knowledge has not yet advanced. A secret lies within this relationship of gland-cell to the efficiency of a nervous impulse, that may prove of the utmost value in explaining the processes of nervous activity. Given the solution of it, the formula of interaction between hormone and nervous impulse may perhaps be found capable of application to other departments of the central nervous system than the sympathetic, and a simple material explanation be obtained for such conditions as spinal neurasthenia. To describe a patient with Addison's disease as suffering from cardio-vascular neurasthenia, or from myasthenia gravis of the circulatory muscles is no wide stretch of the fancy.

The adrenal is, therefore, the ductless gland that promises most in the future to neurologists who seek for deeper acquaintance with the physiological processes of nervous activity. And it has been equally generous to historians of the past. Those who inquire into that most fascinating problem, the origin of the vertebrates, have read in the story of the adrenals clear proof that the thoracico-lumbar or sympathetic system is, in virtue of this reaction, a group distinct from the other visceral nerves, a stratum, so to speak, laid down at a probably later epoch and composed of its own peculiar materials.

As will be seen in the discussion of the thyroid gland, Continental physiologists have accepted this teaching of the English school with regard to the visceral nerves—it is described with admirable clearness in the second edition of Biedl—but at Vienna it has been extended to yield illegitimate conclusions with regard to the functions of the other ductless glands.

The adrenal gland is a compound of cortex with medulla. Both fail in Addison's disease, so that the cardio-vascular sympathetic fault carries with it some expression of the lack of cortical secretion. What that may be is still unknown. The cortical cells do not belong immediately to the sympathetic group; they secrete a doubly refractive fat of complex composition like that of the myelin sheath of nerves, but nothing can be said with regard to its function. However, the presence of this lipoid in abundance indicates a healthy gland. Cushing falls into the error of regarding it as a phenomenon of degeneration, and so an index that the adrenal as well as the pituitary was affected in some of the cases described by him.

Doubtless there are clinical conditions of superadrenalism due to excessive secretion, but they have not been identified, though frequent endeavours have been made to prove that persistently high blood-pressure should be ascribed to this cause.

On the other hand, overgrowth of the cortex in children, producing large adrenal tumours [1], is beyond doubt associated with sexual precocity, premature adolescence, and an early setting of the body, the very opposite of juvenile acromegaly. As a mysterious oddity may be quoted the fact that the human adrenal is distinguished from that of all other animals by a great overgrowth of the cortex in fœtal life; this overgrowth does not occur in cases of hemicephaly, congenital fault that has led to absence of the cerebral hemispheres and reduced the child to the level of the brainless beasts [4].

Simple adenomata of the cortex are very frequent in the adrenal, as they are in the other ductless glands. They cause no pressure symptoms and no clinical phenomena.

THE THYROID GLAND.

In this gland clinical workers first recognised the three main forms of pathological disorder, that have since served as types for the study of changes in the other ductless glands. They are superthyroidism, or Graves's disease; subthyroidism, or myxœdema and cretinism; and adenomata causing pressure symptoms. The adenomata and the parenchymatous goitres are localized or general enlargements of gland tissue, which do not produce secretion proportional to the increase of bulk, and may perhaps be regarded as anatomical evidence that the gland has been striving under adverse conditions to do its proper physiological work.

But there are two chief problems still unsolved, despite much study in the laboratories of experimental research. In the first place arises the question, what is the nature and meaning of the thyroid secretion? Its absence hinders growth, its presence hastens metabolism; with either change curious and special nervous phenomena are seen. Secondly, analysis is perplexed by the double nature of the gland. All the ductless glands, pituitary, adrenal, thyroid, pancreas, and testicle, present this difficulty; two types of cells living in close neighbourhood, often under the same roof, and yet with no obvious reason why they should have chosen such a union.

The associate of the thyroid is the smaller group of parathyroid glands. To them, but without sufficient proof, has been ascribed the train of nervous symptoms that appear when the thyroid is removed. The leading feature of this condition of tetany is an exaggerated excitability of the skeletal muscles through their motor nerves. Many workers have proved that calcium salts in general lower neuro-muscular irritability, and the deduction led to the observation that after removal of the thyroid and parathyroids there is an excessive loss of calcium from the body, a so-called calcium diabetes [9]. This, however, does not seem to be the full explanation of the trouble, for while calcium salts allay tetany after removal of the thyroid, they do not serve to prolong life. Further, it has been urged, but without the least attempt at proof, that all forms of tetany are due to subparathyroidism; and that even myotonia congenita and paralysis agitans are caused by a slow, progressive diminution of parathyroid secretion, while myasthenia gravis is the result of excessive parathyroid activity. This is pretty imagining, but at present bears no relation to substantial fact.

Even with regard to the first question, what is the meaning of the thyroid secretion, little definite can be said. The view that it is required to neutralise certain poisons formed in the metabolism of the body has now few adherents. It is admitted that the thyroid secretes into the blood some substance which influences the heart and the nervous system and growth; that is, it produces one of Starling and Bayliss's hormones, belonging to the same group of simple though potent non-protein bodies as adrenalin, pituitrin, and secretin. Now the Viennese school has elaborated a doctrine with regard to the hormones that is essentially inspired by Ewald Hering's theory of nervous control. The first instances observed of the activity of these bodies were naturally those of stimulation, where a muscle was made to contract or a gland cell to secrete, as in the original discovery of the action of secretin on the pancreas. But adrenalin inhibits some muscles while it causes contraction of others. Hence is deduced the view that a hormone may be purely inhibitory, and, according to Hering's view of inhibition, is therefore a chemical agent which excites an assimilatory process in other organs—in other words, it causes growth. Out of this philosophical analysis of assimilatory and dissimilatory, or inhibiting and exciting hormones, and from a conjectural relationship of the ductless glands to other parts of the visceral nervous system corresponding to the proved association between the adrenals and the sympathetic, have arisen curiously intricate statements of function. They are chiefly taught by Falta and other clinical investigators in Vienna, and they are quoted repeatedly in Biedl's book.

Thus (p. 420) removal of the pancreas removes an inhibitory hormone which it is supposed to form, and consequently the thyroid finds the tissues freed from this constraint and can exert without hindrance its power to accelerate metabolism by its own dissimilatory hormone. Reference will be made again later to this attractive study of the balancing of the body within as well as without, the view that just as our equipoise in standing or in walking depends on the adjustment of nervous impulses, motor and also, as Sherrington has so brilliantly shown, inhibitory towards the many muscles concerned in the posture, so, too, the equilibrium of metabolism and the delicate adjustments of growth, that so marvellously round the whole into the symmetry of adult life, are evidence that the balance of power is fairly adjusted in the concert of the ductless glands, and that no hormone precludes his fellow from a place in the sun of vital growth.

The theory enunciated by Falta and Rudinger as to the actual function of the thyroid secretion is this. Thyroid and parathyroid oppose one another; the former stimulates the sympathetic nerves, the latter inhibits them. Pancreas is associated with parathyroid in retarding metabolism, while thyroid and adrenals augment it. Hence loss of the thyroid leads to:—

(1) Loss of its secretion, and therefore slowed metabolism.

(2) Absence of stimulation of the adrenals.

(3) Escape of the pancreas from inhibition.

(4) Decreased excitability of the nerve which is supposed to innervate the thyroid, that is the vagus, in all its area of distribution.

All this is visionary, and a discussion of it would be profitless at present. More facts are wanted.

PLURIGLANDULAR INSUFFICIENCY.

Increasing emphasis has been laid in the last few years on the need to look upon the ductless glands as parts of a connected whole, so that one gland can neither fall out by the wayside nor grow tenfold in bulk without the others showing consequent change. Careless clinical analysis is apt to accept this readily, and, beneath the ugly phrase of "polyglandular syndrome," to cover ignorance of the cause of pigmentation, of obesity, glycosuria, or gigantism by a general reference to some one or other in the ring of ductless glands, of which nothing is known with certainty.

But the original view of the matter has good justification. The ductless glands do bear some functional relationship one to another;

normal health and growth swing in the equal balance of their activities, and damage of one is likely to result in altered action of another, so that the ultimate bodily change shows the plus of B as well as the minus of A. To name a few common features, which suggest a common bond:—

(1) Carbohydrate metabolism is influenced by all. On ordinary diet sugar appears in the urine when the pancreas is damaged; in exophthalmic goitre, when the thyroid is over active; in acromegaly, that is presumably with superpituitarism; and lastly, by injection of adrenalin or stimulation of the splanchnic nerves to the adrenals. On the other hand, sugar tolerance is exhibited by patients with subglandular conditions of pituitary, thyroid, or adrenal. The correlation may be explained directly or indirectly. Thus in exophthalmic goitre the state of nervous fright may be exciting the adrenals through the splanchnics and so leading to glycosuria; that is, the fright is due to the thyroid, and the glycosuria is a secondary expression of this.

(2) Bodily growth and general metabolism. With the development of the testicle, especially of its interstitial cells, the individual is consolidated and longitudinal growth checked. This process is accelerated to an amazing degree when the cortex of the adrenal is hypertrophied; it is arrested in the dwarfish cretin with atrophied thyroid, and sexual ability fails alike with the acromegalic giant and with obese examples of subpituitarism.

(3) Nervous implications are less obvious. Tetany is a result of sudden thyroid or parathyroid loss. There is nothing corresponding to the clear connexion of the adrenal medulla with the sympathetic nervous impulses.

(4) Association between the glands themselves. The pituitary becomes hypertrophied when the thyroid is removed. Acromegaly frequently leads, in its later stages, to enlargement of the thyroid. Thyroid extract is found to be a useful remedy in acromegaly, even for the amblyopia of that disease.

(5) The double anatomical constitution of all the glands is a morphological chance that does not enter into the question. So, too, no stress can be laid upon the fact that an active principle of simple molecular constitution, which is not destroyed by boiling, can be extracted from the adrenal, the pituitary, and apparently from the thyroid and pancreas.

The adrenal cortex and the interstitial cells of the testicle secrete a special fatty substance; the thyroid and pituitary a special colloid. But the lipoid and the colloid are probably different substances in each case. Certainly that of the pituitary does not contain iodine.

(6) Morphological relationship. This argument, when it can be applied, is one of great weight to emphasize a likeness of function. But the work done in comparative physiology and that in morphology is accumulated in separate islands of thought, and few have sought to cross the estranging sea. Gaskell, on morphological grounds [6] classifies together the pituitary, thyroid, and adrenal cortex as being all modified from the coxal glands, that is the segmental excretory apparatus of some primitive arthropod type. This suggests that these ductless glands may be found to have physiological activities that are more closely related to each other than some workers would at present care to admit.

Indeed the question of the relationship to one another of the ductless glands is one of subtle intricacy, which needs the clearest thought and more proved facts for a right judgment to be made. Hypotheses serve to direct the search this way and that, and through them more evidence is brought to light and tested. But confusion will disorder all, if theory and analogy be permitted to develop a statement and this be too early accepted as conclusive. The teaching of the Viennese school, despite its brilliant suggestiveness, carries with it that dangerous fault, for it has been elaborated far beyond the facts. There is not a shadow of proof that the thyroid has any special and peculiar relation to the vagus nerve, like that of the adrenals to the sympathetic. Drugs, such as pilocarpine and atropine, cannot be classified with regard to their action upon different departments of the nervous system as rigidly as can adrenalin. Rightly to explain clinical observations is hard enough, even when one uses the proved truths of physiology and pathology; error is unavoidable, if the deduction is made from error. The apparent simplicity of a generalization will always recommend it to medicine, impatient for aid to comprehend the instant problems of disease. But the speculative nature of Falta's views should be properly appreciated, lest on them too much be built and much weary work of reconstruction be called for later, if the foundations fail.

The essential facts and the broad laws concerned with the activities of the visceral nervous system have been mainly ascertained by experimental work in England. As it chanced, this study of the visceral nerves was almost hindered in its progress by the necessity of devising at each step experiments to demonstrate the error of a general law which had been formulated in Vienna by von Basch, the law of crossed innervation of the longitudinal and circular coats of plain muscle in hollow viscera. The law was absolutely unproven, but it was so engagingly simple that it was accepted without question as it stood, to be the working creed of many medical writers. Its removal cost much labour, and now the cleared ground is threatened afresh. Medicine owes no debt of gratitude to those who teach to her theories without proof.

Still these views, and particularly Biedl's book, will do good service, insomuch as they emphasize the problems to be solved. We see how widely and deeply the influence of the ductless glands penetrates through the busy factories of life. But the how and the why of it all is chiefly a mystery still. The reading of the riddle must increase man's power to help man.

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PUBLICATIONS RECENTLY RECEIVED.

[*Notes on a book under this heading do not preclude a subsequent review.*]

Die Vasomotorisch-trophischen Neurosen. Eine Monographie. Von Dr. R. CASSIRER. Zweite umgearbeitete und vermehrte Auflage. S. 988, mit 24 Abbildungen im Text und 24 Tafeln. Berlin: Karger, 1912.

This extremely important monograph contains all that is known of the vasomotor and trophic neuroses admirably arranged for reference. The first chapter deals with the anatomy and physiology of vasomotor and secretory mechanisms, and with the trophic functions of the nervous system; acroparæsthesia, erythromelalgia, Raynaud's disease, acro-asphyxia chronica, sclerodermia, acute local œdema, and multiple neuropathic gangrene of the skin, are all treated in a series of chapters, each of which is a monograph in itself. The list of papers alluded to in the various chapters occupies nearly 100 pages and is admirably arranged, but unfortunately there is no general index. This book is indispensable for every medical library and for all who are interested in the vasomotor and trophic neuroses.

Die klinische Stellung der sogenannten genuinen Epilepsie. Von E. REDLICH und O. BINSWANGER. S. 146. Berlin: Karger, 1913.

The two separate reports presented by Redlich and Binswanger to the meeting of the German Neurological Society at Hamburg in 1912 are reprinted here. Redlich's occupies 124 pages and contains a complete bibliography of the recent and more important papers on epilepsy. He found the definition of his subject "genuine or true epilepsy" very difficult, and suggests that this title should be dropped, but his broad-minded view of the condition generally included in it will be acceptable to most clinicians. The various etiological factors to which the disease may be due, or to which it has been attributed, are fully discussed, and their possible pathological significance is considered. He regards epilepsy as an organic cerebral disease though its essential anatomy is still uncertain. The clinical features of the disease and the mutual relationships of the different clinical forms of epilepsy are also fully considered.

Binswanger deals chiefly with the histological changes found in epileptic brains and their significance, but he still holds that there is no satisfactory evidence that epilepsy is an organic cerebral disease.

L'Aphasie Motrice Pure. Par ANDRÉ PÉLISSIER. Pp. 198. Paris: Vigot Frères, 1912.

The author, a pupil of Dejerine, carried out in the Salpêtrière the clinical and pathological investigations on which this monograph is based. By pure motor aphasia he understands a more or less complete inability to articulate words which is not due to a paresis or ataxia of the muscles of articulation, and is not associated with any disturbance of other elements of speech. He brings this form of speech disturbance into contrast with Broca's aphasia in which internal speech is always effected to some extent, but he admits that a sharp line cannot be drawn between them. Pure motor aphasia may be produced by either cortical or subcortical lesions; the cortical centre (to the disturbance of which it may be due) is apparently always Broca's area.

The monograph can be strongly recommended as a concise and intelligent contribution to the affection of the motor side of speech.

Hysterische Lähmungen; Studien über ihre Pathophysiologie und Klinik. S. 174. Von H. DI GASPERO. Berlin: Julius Springer, 1912.

This book, which is published from the office of the *Zeitschrift für Gesamte Neurologie und Psychiatrie* is an interesting and valuable contribution to the study of isolated hysterical palsies. The clinical symptoms and the nature of the functional disturbances are carefully and elaborately described, but the pages which will probably prove most interesting and instructive are those which deal with the vasomotor state of the affected limbs. The author, by means of the plethysmograph, compared the vascular reactions in the palsied and the corresponding normal limb to various sensory and psychical affects, and was able to demonstrate remarkable differences. Further, he found that the vessels of the abnormal limb reacted differently to the vessels of the normal limb on inhalation of amyl nitrite and adrenalin injections. The book deserves careful study.

Le Ramollissement Cérébral (Étude anatomo-clinique et expérimentale) Diagnostic entre le Ramollissement et l'Encéphalite. Par HENRI SCHAEFFER. Pp. 168. Paris: G. Steinheil, 1910.

The most interesting feature of this monograph is a detailed comparison of the histological changes produced by aseptic and septic emboli of the cerebral vessels. The work was carried out by producing experimental embolism in animals and by pathological observations on the human brain; it contains perhaps little that is new, but the care with which the histological examinations were evidently made and their lucid description recommend the book strongly to all interested in cerebral pathology. The much debated question of the origin of the *corps granuleux* (Körnchenzellen) is fully considered; the author believes they may be derived from the blood, from the vascular connective tissue, or from the neuroglia.

A Clinical Study of Acute Poliomyelitis. By F. W. PEABODY, M.D., GEORGE DRAPER, M.D., and A. R. DOCHEZ, M.D. [Monographs of the Rockefeller Institute for Medical Research.] Pp. 187, with 13 plates. New York: Rockefeller Institute, 1912.

This clinical study is based upon 183 cases of acute poliomyelitis admitted to the Rockefeller Institute. A short account is given of the nature of the virus and the pathological anatomy of the disease, but the greater part of the book is devoted to an analysis of its clinical manifestations. The authors divide their cases into three groups: the abortive form where the infection does not result in paralysis; the rare cerebral group which ends in spastic paralysis; and, lastly, the bulbo-spinal group which contains the majority of cases. The case-reports are admirably full and clear, and the illustrations excellent.

Selected Papers on Hysteria and Other Psychoneuroses. By Professor SIGMUND FREUD. Second Edition, translated by A. A. Brill, M.D. Pp. 215. New York: Journal of Nervous and Mental Diseases Publishing Company, 1912.

This is a second English edition of Freud's collected papers. It contains the original preliminary communication on the "Psychic Mechanism of Hysterical Phenomena," written in conjunction with Breuer. This is followed by the story of "Lucy R.," in which is laid bare the origin of certain hallucinations of smell, and the well-known case of hysterical pains in the legs, "Elizabeth v. R." The next chapter, on the "Psychotherapy of Hysteria," reveals the lines along which Freud developed after separation from Breuer, and after he had given up hypnosis as a necessary preliminary to analysis treatment. Then follows a chapter on the "Defence Neuropychoses" in which the theory of phobias and obsessions as protective reactions is laid down, and, after a short statement of Freud's views on the rôle of sexuality in the etiology of the neuroses, the book ends with a paper concerning "wild," or, as we should say, "far-fetched," psycho-analysis. All who are anxious to learn the views of Freud himself, as opposed to those of his followers, should study this book, which contains the best of his papers. The translation is on the whole remarkably good.

Les Syncinésies. Par le Docteur G. STROEHLIN. Pp. 147. Paris: G. Steinheil, 1911.

This is a study of associated movements and the various conditions under which they may appear. After alluding to the impossibility of rotating the hands in opposite directions, and other similar associated movements in normal human beings, the author considers their appearance in "*débilité motrice*," a term which signifies any condition accompanied by diminished inhibitory action on the part of the pyramidal tract. He concludes that in primitive stages of development, movements were bilateral and symmetrical, and that during certain pathological conditions, such as infantile hemiplegia or adult hemiparesis, this bilateral character may reappear. Such associated movements occur solely in high pyramidal lesions and not with spinal or peripheral paralysis; they are the consequence of defective cortical inhibition on the side of the lesion, combined with over-action of the opposite cortex.

Manisch-depressives und periodisches Irresein als Erscheinungsform der Katatonie. Eine Monographie. Von Dr. MAURYCY URSTEIN. S. 650. Berlin, Wien: Urban und Schwarzenberg, 1912.

This book is written in continuation of the author's previous work on dementia præcox [*vide* BRAIN, 1909, vol., xxxii., p. 482]. It consists mainly of a series of most elaborate clinical histories extending in some cases over thirty to forty years. This long-continued observation was possible owing to the excellent system of case-reports initiated by Heinrich Laehr at Schweizenhof Asylum in Zehlendorf; these admirable notes were given over to the author for study by the present superintendent. Each report ends in a summary description of the case, and the conclusions to be drawn from it. In the last hundred pages, the author sums up the symptoms, causes and prognosis in katatonia, and lays stress on the thesis, that maniacal depressive and circular psychoses may be phenomena of dementia præcox.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I. to XXIII. inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

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